

Use Of GAL3 Receptor Antagonists For The Treatment Of  
Depression And/Or Anxiety And Compounds Useful in Such  
Methods

5 Background of the Invention

This application claims the benefit of U.S. Provisional  
Application No. 60/265,586, filed January 31, 2001, the  
contents of which is incorporated by reference into the  
10 subject application.

Throughout this application, various publications are  
referenced in parentheses by author and year. Full  
citations for these references may be found at the end of  
15 the specification immediately preceding the claims. The  
disclosures of these publications in their entireties are  
hereby incorporated by reference into this application to  
describe more fully the art to which this invention  
pertains.

20 Depression is the most common of mental disorders and yet  
is often underdiagnosed and undertreated, inflicting  
substantial morbidity and psychosocial impairment on its  
sufferers. Depression is mainly characterized by sadness,  
25 flatness, loss of feeling, anhedonia (lack of pleasure),  
tearfulness, agitation or retardation, thoughts of guilt,  
and worthlessness; in severe cases, suicide,  
hallucinations and delusions.

30 Depression can be mainly categorized into bipolar  
disorders, identifying wide swings of mood; major  
depressive illness, marked by severe depressive symptoms

other psychiatric disorder. But by far the strongest comorbidities in both cases are between depression and anxiety disorders. Therefore, it is now becoming common clinical practice to treat both indications with antidepressants such as SSRIs.

The key clinical features of anxiety disorders relate to various combinations of psychological and physical manifestations of anxiety, not attributable to real danger and occurring either in attacks (panic disorder - PD) or as a persisting state (generalized anxiety disorder - GAD). Other neurotic features may be present (obsessional or hysterical symptoms) but do not dominate the clinical picture.

15

#### The Pathophysiology of Depression

Theories underlying the pathophysiology of depression have developed from several lines of evidence including:

- 1) changes in neurotransmitter monoamine levels;
- 2) endocrine imbalance; and
- 3) electrophysiological studies on sleep functions.

Evidence implicating the role of neurotransmitters in depression, in particular the monoamines serotonin, noradrenaline and dopamine, include the success of pharmacological agents in treating depressive disorders. Many of the tricyclic antidepressants (TCAs), selective serotonin re-uptake inhibitors (SSRIs) and monoamine oxidase inhibitors (MAOIs) effective in the treatment of depression increase the availability of the catecholamines (noradrenaline and dopamine) and indolamines (serotonin) in the central nervous system

(CNS). The clinical efficacy of these agents has given rise to the catecholamine-indolamine hypothesis of depression. This theory postulates that a certain level of amines and/or receptor sensitivity to catecholamines functions to generate a normal mood. A receptor insensitivity, a depletion of monoamines, or a decrease in their release, synthesis or storage have been postulated to lead to depression.

10 Current Treatments for Depression

A variety of pharmacological agents have been employed to treat depression based on the catecholamine-indolamine hypothesis of depression. Drugs used to treat depression include MAOIs, atypical antipsychotics, lithium, TCAs, and SSRIs. In addition, a number of off-label agents such as antiepileptics are used to treat depression in treatment-resistant patients.

Tricyclic antidepressants are about equal to SSRIs in effectiveness against depression thus providing supporting evidence for the catecholamine-indolamine hypothesis of depression. However, SSRIs have largely displaced TCAs because of side effects associated with TCAs and the need to monitor EKG and plasma drug concentration. Although the SSRIs are viewed as an improvement over other antidepressants, they are not without their clinical problems. Adverse effects on sexual function, primarily anorgasmia and delayed ejaculation, have been consistently reported. Other, common side-effects include sleep disorders, yawning, weight changes, suicidal ideation and extrapyramidal-like side-effects such as dystonic reactions. Thus, there

clearly remains a medical need for new treatments of depression, without the adverse side-effect profile of existing agents and with improved efficacy.

5 Current treatments for anxiety

There is now considerable direct evidence for the efficacy of the SSRIs both in depression and in anxiety disorders.

10

Of the current SSRIs approved for marketing in the USA all have shown sufficient efficacy to be further approved for the treatment of at least one anxiety disorder, for example; obsessive compulsive disorder (OCD) and  
15 generalized anxiety disorder (GAD). Compounds such as paroxetine and sertraline are also indicated for the treatment of panic disorder (PD).

However, it is clear from the issues raised earlier  
20 relating to the efficacy and side-effect profile of SSRIs and for that matter the more widely prescribed benzodiazapines, there still exists a real medical need for novel approaches for the treatment of anxiety and depression.

25

Discovery Of GAL3 Receptor Subtype And Its Role In Depression and Anxiety

The investigations leading to the present invention arose from the discovery that mRNA for the GAL3 receptor is  
30 localized to areas of the rat brain associated with mood and emotion (see PCT International Publication No. WO 98/15570, published April 16, 1998), thus supporting the



expression of GAL3 in those regions. Protein for the GAL3 receptor is also shown to localize to areas of the rat brain associated with mood and emotion (see Table 11 and discussion herein).

5

This discovery led to the hypothesis that the GAL3 receptor may play a role in controlling the activity of catecholamine and indolamine neurons in the CNS. Galanin is known to hyperpolarize neurons, including  
10 monoaminergic neurons (Seutin, et al., 1989) and to have inhibitory effects on 5-HT neurons (Xu, et al., 1998), and dopamine neurons (Gopalan, et al., 1993; De Weille, et al., 1989; Jansson, et al., 1989; Nordstrom, et al., 1987; Weiss, et al., 1998). In light of these reports, a  
15 series of in vivo behavioral experiments were carried out to evaluate the antidepressant properties of a selective GAL3 receptor antagonist. The rat Forced Swim Test and the rat Social Interaction Test were employed to evaluate the use of selective GAL3 receptor antagonists to treat  
20 depression and anxiety. These models are considered by experts in the field to reflect the potential of agents to treat depression and anxiety.

#### Rat Forced Swim Test (FST)

25 The rat Forced Swim Test (FST) is a behavioral test that is used to screen compounds for antidepressant efficacy (Porsolt et al., 1977, 1978; Porsolt, 1981). This test is widely used as it is reliable across laboratories, relatively easy to perform and is sensitive to the  
30 effects of some of the major classes of antidepressant drugs, including TCAs and MAOIs, and various atypical antidepressants. Furthermore, this test is relatively

selective for antidepressant drugs, as few psychoactive drugs produce similar behavioral actions in the FST.

In the rat FST, animals are placed in a cylinder of water, from which there is no escape, for an extended period of time. Typically, animals will display a range of behaviors such as immobility, climbing, swimming, and diving, with immobility being predominant after several minutes of immersion in the water. Consequently, many past studies have only measured or scored immobility after the administration of the test agent. Unfortunately, this method does not score any other active behaviors that may be produced by potential antidepressants. Thus, if a particular class of antidepressant were to have very little effect on immobility, yet produce characteristic behaviors during the FST, these behaviors would not be scored and the conclusion would be that the compound in question does not possess antidepressant action.

Recently, however, a sampling technique was developed to score active behaviors in the FST, such as swimming, climbing and diving, in addition to immobility (Detke, et al., 1995; Lucki, 1997; Page, et al., 1999; Renner and Lucki, 1998). This modified sampling technique has indicated that SSRIs, such as fluoxetine, paroxetine and sertraline, significantly decrease immobility and increase swimming time (Detke, et al., 1995; Page, et al., 1999). In contrast, selective reuptake inhibitors of norepinephrine (NE) increase climbing behavior but do not alter swimming time (Detke, et al., 1995; Page, et al., 1999).

### Rat Social Interaction Test (SIT)

There are a number of paradigms that have been used to determine whether a compound possesses anxiolytic action.

5 A number of these tests involve food or water deprivation, punishment or measurement of consummatory behavior (see File, et al., 1980; File, 1985; Rodgers, et al., 1997; and Treit, 1985, for review). In addition, in these models, prior conditioning reduces the uncertainty  
10 or anxiety. In general, these tests lack ethological validity.

One model that is based upon an unconditioned response that does not involve punishment or deprivation is the  
15 Social Interaction Test (SIT) (File and Hyde, 1978, 1979). In this model, rats previously housed singly are placed in a familiar, dimly lit, test arena with weight-matched, novel partners. The principal anxiogenic stimulus under these conditions is the partner novelty,  
20 which involves an unconditioned response to a potential threat. After pharmacological treatments, the following behaviors are scored as active social interaction: grooming, sniffing, biting, boxing, wrestling, following, crawling over and crawling under. A wide range of  
25 psychoactive drugs have been examined in this paradigm and it has been shown that the social interaction test can distinguish anxiolytics from antidepressants, antipsychotics, analeptics and sedative agents (File, 1985; Guy and Gardner, 1985). This test can detect  
30 anxiolytic agents such as the benzodiazepines (File and Hyde, 1978; File and Hyde, 1979; File, 1980), in addition to non-benzodiazepines, including paroxetine and other

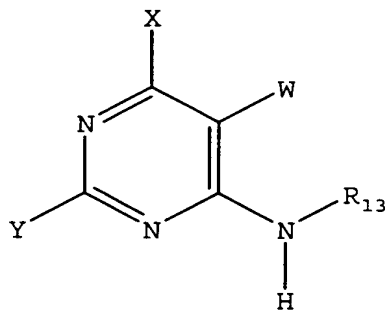
SSRIs (Lightowler, et al., 1994). Finally, the social interaction test can detect anxiogenic agents, including the inverse benzodiazepine receptor agonists (File, et al., 1982; File and Pellow, 1983; File and Pellow, 1984; 5 File, 1985).

In an embodiment of the present invention the synthesis of novel pyrimidines which bind selectively to the cloned human GAL3 receptor, compared to other cloned human G-  
10 protein coupled receptors, as measured in *in vitro* assays, is disclosed. In a further embodiment of the present invention the synthesis of indolones which bind selectively to the cloned human GAL3 receptor, compared to other cloned human G-protein coupled receptors, as  
15 measured in *in vitro* assays, is disclosed. The *in vitro* receptor assays described hereinafter were performed using various cultured cell lines, each transfected with and expressing only a single galanin-type receptor.

20 From the binding information described hereinafter, it has unexpectedly been discovered that compounds which are specific for the human GAL3 receptor with a binding affinity greater than ten-fold higher than the binding affinity with which the compounds bind to a human GAL1  
25 receptor are effective in animal models of depression and anxiety which are predictive of efficacy in humans. Thus, we demonstrate that the GAL3 receptor antagonists, which may be classified as neutral antagonists, inverse agonists or allosteric modulators, provide a novel  
30 method to treat depressive disorders and/or anxiety.

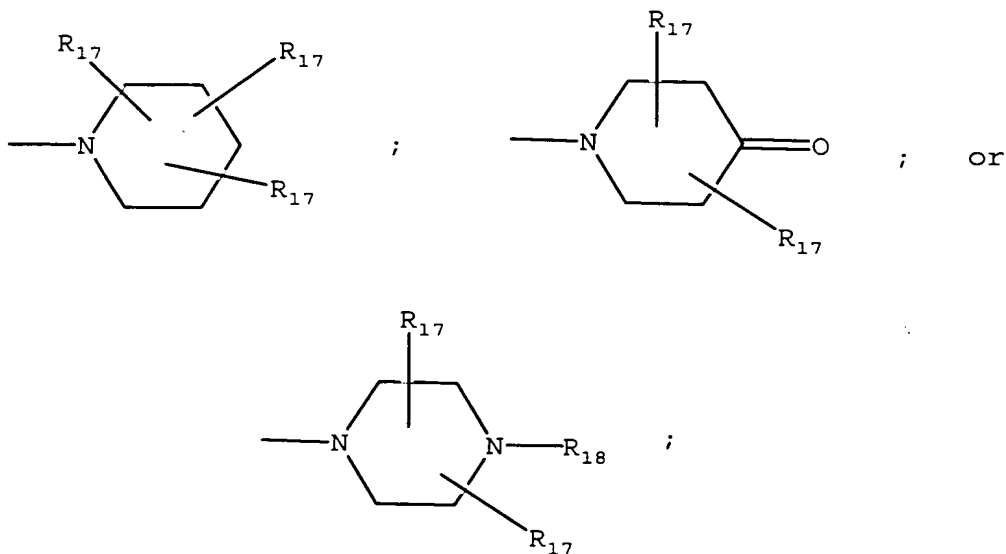
Summary of the Invention

The present invention provides a method of treating a subject suffering from depression which comprises administering to the subject an amount of compound effective to treat the subject's depression wherein the compound has the structure:



wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

wherein X is;  $\text{NR}_{11}\text{R}_{12}$ ;



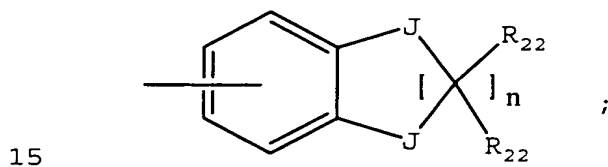
wherein  $\text{R}_{11}$  is H, straight chained or branched  $\text{C}_1\text{-C}_7$  alkyl,  $(\text{CH}_2)_q\text{-O-(CH}_2)_m\text{-CH}_3$ , aryl, or aryl  $(\text{C}_1\text{-C}_6)$  alkyl;

wherein  $R_{12}$  is straight chained or branched  $C_1$ - $C_7$  alkyl,  $(CH_2)_q-O-(CH_2)_m-CH_3$ , or  $-(CH_2)_m-Z$ ;

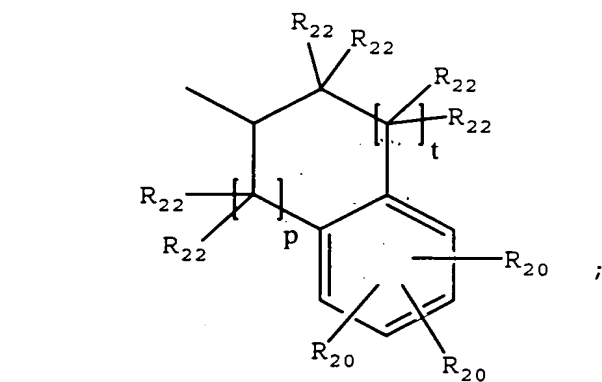
5 wherein  $R_{13}$  is a bicyclic alkyl ring system, adamantyl, noradamantyl,  $C_3$ - $C_{10}$  cycloalkyl, heteroaryl, aryl, aryl( $C_1$ - $C_6$ )alkyl,  $Q_1$  or  $Q_2$ ;

10 wherein aryl may be substituted with one or more  $C_1$ - $C_{10}$  straight chained or branched alkyl, aryl, heteroaryl, or  $N(R_{19})-Z$ ;

wherein  $Q_1$  is



wherein  $Q_2$  is

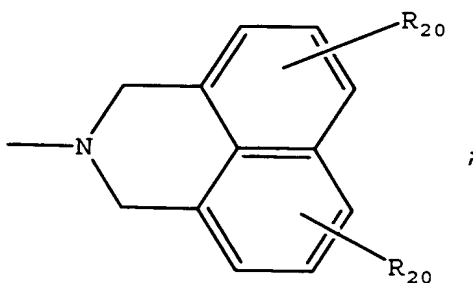
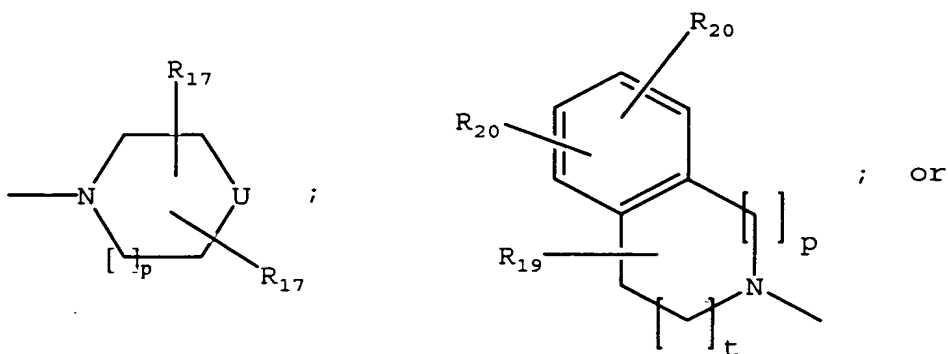


wherein each J is independently O, S,  $C(R_{22})_2$  or  $NR_4$ ;

wherein  $R_4$  is H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$  cycloalkenyl or aryl;

5

wherein Y is  $NR_{14}R_{15}$ ;



10

wherein  $R_{14}$  is H, straight chained or branched  $C_1$ - $C_6$  alkyl,  $(CH_2)_q-O-(CH_2)_m-CH_3$ ,  $C_3$ - $C_6$  cycloalkyl, or  $(C(R_{19})_2)_m-Z$ ;

15

wherein  $R_{15}$  is straight chained or branched  $C_3$ - $C_6$  alkyl,  $(CH_2)_q-O-(CH_2)_m-CH_3$ ,  $C_3$ - $C_6$  cycloalkyl,  $(C(R_{19})_2)_mN(R_{16})_2$  or  $(C(R_{19})_2)_m-Z$ ;

20

wherein  $R_{16}$  is straight chained or branched  $C_1$ - $C_7$  alkyl, straight chained or branched  $C_1$ - $C_7$  monofluoroalkyl,

straight chained or branched  $C_1-C_7$  polyfluoroalkyl, straight chained or branched  $C_2-C_7$  alkenyl, straight chained or branched  $C_2-C_7$  alkynyl,  $C_5-C_7$  cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_q-O-(CH_2)_m-CH_3$ ;

5

wherein each  $R_{17}$  is independently H;  $-OR_{21}$ ,  $-OCOR_{21}$ ,  $-COR_{21}$ ,  $-NCOR_{21}$ ,  $-N(R_{21})_2$ ,  $-CON(R_{21})_2$ ,  $-COOR_{21}$ , straight chained or branched  $C_1-C_7$  alkyl, straight chained or branched  $C_1-C_7$  monofluoroalkyl, straight chained or branched  $C_1-C_7$  polyfluoroalkyl, straight chained or branched  $C_2-C_7$  alkenyl, straight chained or branched  $C_2-C_7$  alkynyl,  $C_5-C_7$  cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_n-O-(CH_2)_m-CH_3$ ;

10

wherein  $R_{18}$  is straight chained or branched  $C_1-C_6$  alkyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_q-O-(CH_2)_m-CH_3$ ;

15

wherein each  $R_{19}$  is independently H, or straight chained or branched  $C_1-C_6$  alkyl;

wherein each  $R_{20}$  is independently -H; straight chained or branched  $C_1-C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2-C_7$  alkenyl or alkynyl;  $C_3-C_7$  cycloalkyl or  $C_5-C_7$  cycloalkenyl; -F, -Cl, -Br, or -I;  $-NO_2$ ;  $-N_3$ ; -CN;  $-OR_{21}$ ,  $-OCOR_{21}$ ,  $-COR_{21}$ ,  $-NCOR_{21}$ ,  $-N(R_{21})_2$ ,  $-CON(R_{21})_2$ , or  $-COOR_{21}$ ; aryl or heteroaryl; or two  $R_{20}$  groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

25

wherein each  $R_{21}$  is independently -H; straight chained or branched  $C_1-C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2-C_7$  alkenyl or alkynyl;  $C_3-C_7$  cycloalkyl,  $C_5-C_7$  cycloalkenyl, aryl, or aryl( $C_1-$

30



C<sub>6</sub>)alkyl;

wherein each R<sub>22</sub> is independently H, F, Cl or C<sub>1</sub>-C<sub>4</sub> straight chained or branched alkyl;

5

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

10

wherein p is an integer from 0 to 2 inclusive;

wherein q is an integer from 2 to 4 inclusive;

wherein t is 1 or 2;

15

wherein U is O, -NR<sub>16</sub>, S, C(R<sub>17</sub>)<sub>2</sub>, or -NSO<sub>2</sub>R<sub>16</sub>;

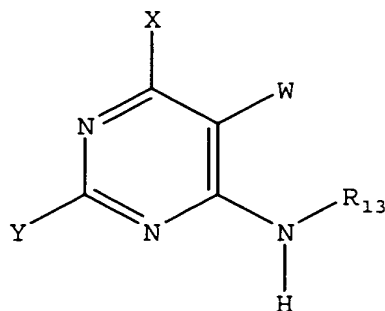
wherein Z is C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>4</sub>-C<sub>7</sub> cyclic ether, C<sub>4</sub>-C<sub>7</sub> cyclic thioether, aryl, or heteroaryl; or

20

a pharmaceutically acceptable salt thereof.

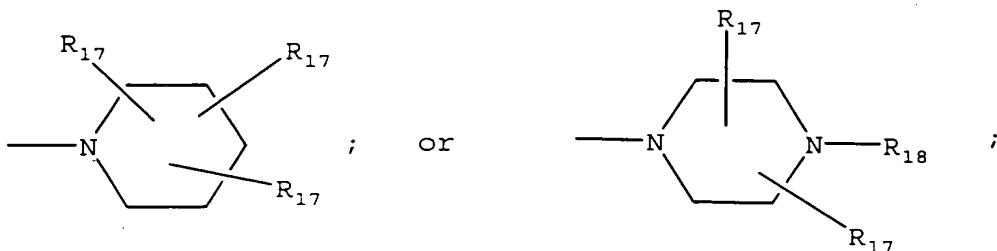
25

The present invention provides a method of treating a subject suffering from depression which comprises administering to the subject an amount of compound effective to treat the subject's depression wherein the compound has the structure:



wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

5 wherein X is  $\text{NR}_{11}\text{R}_{12}$ ;



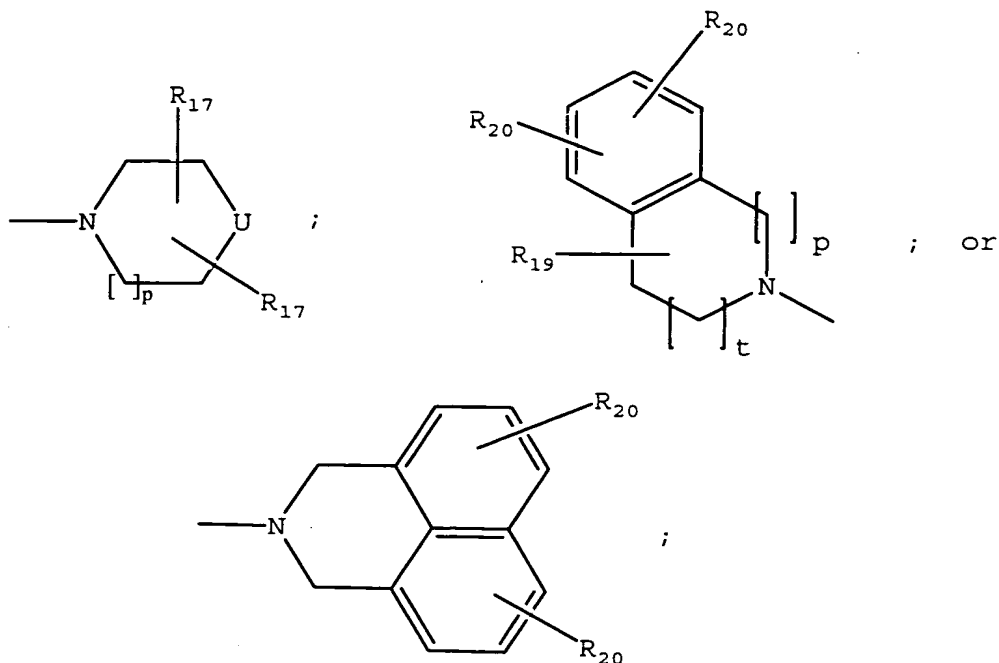
wherein  $\text{R}_{11}$  is H, straight chained or branched  $\text{C}_1\text{-C}_7$  alkyl,  $(\text{CH}_2)_q\text{-O-(CH}_2)_m\text{-CH}_3$ , aryl or aryl( $\text{C}_1\text{-C}_6$ )alkyl;

10 wherein  $\text{R}_{12}$  is straight chained or branched  $\text{C}_1\text{-C}_7$  alkyl,  $(\text{CH}_2)_q\text{-O-(CH}_2)_m\text{-CH}_3$ , or  $\text{-(CH}_2)_m\text{-Z}$ ;

wherein  $\text{R}_{13}$  is a bicyclic alkyl ring system, aryl or aryl( $\text{C}_1\text{-C}_6$ )alkyl;

15

wherein Y is  $\text{NR}_{14}\text{R}_{15}$ ;



wherein  $R_{14}$  is H, straight chained or branched  $C_1$ - $C_6$  alkyl,  $(CH_2)_q$ -O- $(CH_2)_m$ - $CH_3$ ,  $C_3$ - $C_6$  cycloalkyl, or  $(C(R_{19})_2)_m$ -Z;

5

wherein  $R_{15}$  is straight chained or branched  $C_3$ - $C_6$  alkyl,  $(CH_2)_q$ -O- $(CH_2)_m$ - $CH_3$ ,  $C_3$ - $C_6$  cycloalkyl, or  $(C(R_{19})_2)_m$ -Z;

wherein U is O,  $-NR_{16}$ , S,  $C(R_{17})_2$ , or  $-NSO_2R_{16}$ ;

10

wherein Z is  $C_3$ - $C_{10}$  cycloalkyl, aryl, or heteroaryl;

wherein  $R_{16}$  is straight chained or branched  $C_1$ - $C_7$  alkyl, straight chained or branched  $C_1$ - $C_7$  monofluoroalkyl, straight chained or branched  $C_1$ - $C_7$  polyfluoroalkyl, straight chained or branched  $C_2$ - $C_7$  alkenyl, straight chained or branched  $C_2$ - $C_7$  alkynyl,  $C_5$ - $C_7$  cycloalkenyl,  $-(CH_2)_m$ -Z, or  $(CH_2)_q$ -O- $(CH_2)_m$ - $CH_3$ ;

15

wherein each  $R_{17}$  is independently H;  $-OR_{21}$ ,  $-OCOR_{21}$ ,  $-COR_{21}$ ,  $-NCOR_{21}$ ,  $-N(R_{21})_2$ ,  $-CON(R_{21})_2$ ,  $-COOR_{21}$ , straight chained or branched  $C_1$ - $C_7$  alkyl, straight chained or branched  $C_1$ - $C_7$  monofluoroalkyl, straight chained or branched  $C_1$ - $C_7$  polyfluoroalkyl, straight chained or branched  $C_2$ - $C_7$  alkenyl, straight chained or branched  $C_2$ - $C_7$  alkynyl,  $C_5$ - $C_7$  cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_n-O-(CH_2)_m-CH_3$ ;

wherein  $R_{18}$  is straight chained or branched  $C_1$ - $C_6$  alkyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_q-O-(CH_2)_m-CH_3$ ;

wherein each  $R_{19}$  is independently H, or straight chained or branched  $C_1$ - $C_6$  alkyl;

wherein each  $R_{20}$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl or  $C_5$ - $C_7$  cycloalkenyl; -F, -Cl, -Br, or -I;  $-NO_2$ ;  $-N_3$ ; -CN;  $-OR_{21}$ ,  $-OCOR_{21}$ ,  $-COR_{21}$ ,  $-NCOR_{21}$ ,  $-N(R_{21})_2$ ,  $-CON(R_{21})_2$ , or  $-COOR_{21}$ ; aryl or heteroaryl; or two  $R_{20}$  groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each  $R_{21}$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$  cycloalkenyl, aryl or aryl( $C_1$ - $C_6$ )alkyl;

wherein each  $m$  is an integer from 0 to 4 inclusive;

wherein each  $n$  is an integer from 1 to 4 inclusive;

wherein p is an integer from 0 to 2 inclusive;

wherein q is an integer from 2 to 4 inclusive;

5

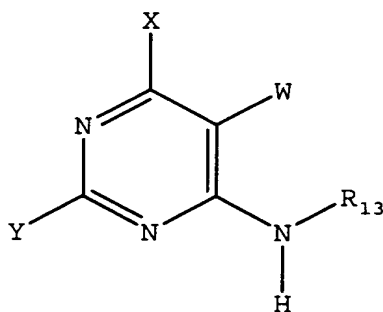
wherein t is 1 or 2; or

a pharmaceutically acceptable salt thereof.

10

The present invention provides a method of treating a subject suffering from depression which comprises administering to the subject an amount of compound effective to treat the subject's depression wherein the compound has the structure:

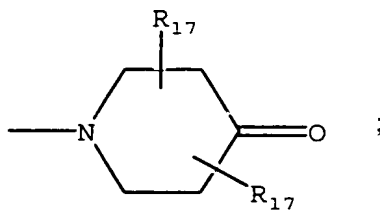
15



wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

20

wherein X is N(CH<sub>3</sub>)<sub>2</sub> or



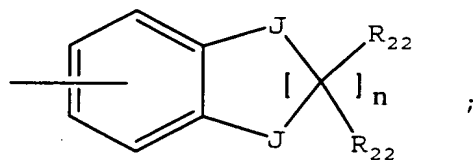
wherein  $R_{13}$  is an aryl, adamantyl, noradamantyl,  $C_3$ - $C_{10}$  cycloalkyl, heteroaryl,  $Q_1$  or  $Q_2$ ;

5

wherein aryl may be substituted with one or more  $C_1$ - $C_{10}$  straight chained or branched alkyl, aryl, heteroaryl, or  $N(R_{19})-Z$ ;

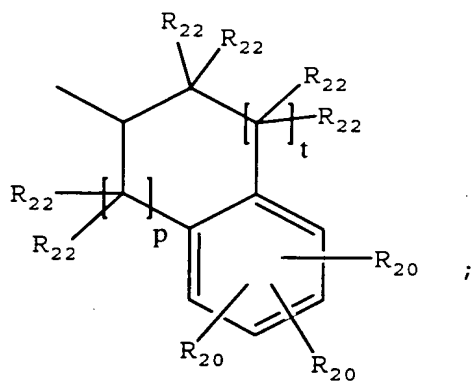
10

wherein  $Q_1$  is



wherein  $Q_2$  is

15

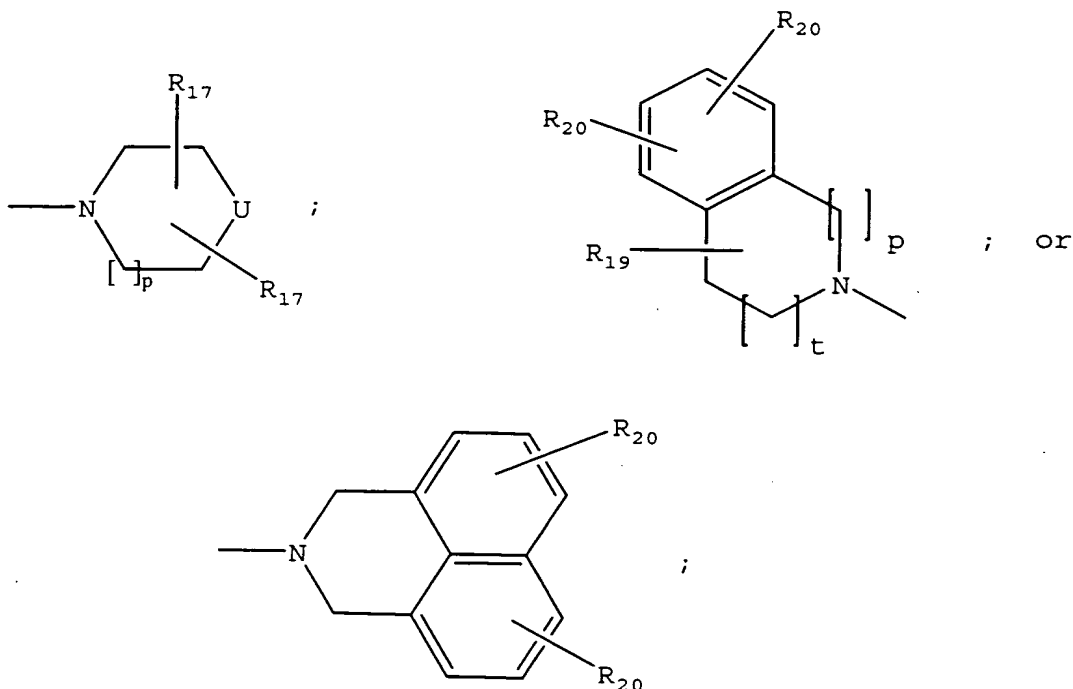


wherein each  $J$  is independently  $O$ ,  $S$ ,  $C(R_{22})_2$  or  $NR_4$ ;

wherein  $R_4$  is -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$  cycloalkenyl or aryl;

5

wherein Y is  $NR_{14}R_{15}$ ;



10 wherein  $R_{14}$  is H, straight chained or branched  $C_1$ - $C_6$  alkyl,  $(CH_2)_q-O-(CH_2)_m-CH_3$ ,  $C_3$ - $C_6$  cycloalkyl, or  $(C(R_{19})_2)_m-Z$ ;

wherein  $R_{15}$  is straight chained or branched  $C_3$ - $C_6$  alkyl,  $(CH_2)_q-O-(CH_2)_m-CH_3$ ,  $C_3$ - $C_6$  cycloalkyl, or  $(C(R_{19})_2)_m-Z$ ;

15

wherein U is O,  $-NR_{16}$ , S,  $C(R_{17})_2$ , or  $-NSO_2R_{16}$ ;

wherein Z is  $C_3$ - $C_{10}$  cycloalkyl, aryl, or heteroaryl;

wherein  $R_{16}$  is straight chained or branched  $C_1$ - $C_7$  alkyl, straight chained or branched  $C_1$ - $C_7$  monofluoroalkyl, straight chained or branched  $C_1$ - $C_7$  polyfluoroalkyl, straight chained or branched  $C_2$ - $C_7$  alkenyl, straight chained or branched  $C_2$ - $C_7$  alkynyl,  $C_5$ - $C_7$  cycloalkenyl, -  
 5  $(CH_2)_m-Z$ , or  $(CH_2)_q-O-(CH_2)_m-CH_3$ ;

wherein each  $R_{17}$  is independently H;  $-OR_{21}$ ,  $-OCOR_{21}$ ,  $-COR_{21}$ ,  $-NCOR_{21}$ ,  $-N(R_{21})_2$ ,  $-CON(R_{21})_2$ ,  $-COOR_{21}$ , straight chained or branched  $C_1$ - $C_7$  alkyl, straight chained or branched  $C_1$ - $C_7$  monofluoroalkyl, straight chained or branched  $C_1$ - $C_7$  polyfluoroalkyl, straight chained or branched  $C_2$ - $C_7$  alkenyl, straight chained or branched  $C_2$ - $C_7$  alkynyl,  $C_5$ - $C_7$  cycloalkenyl, -  
 10  $(CH_2)_m-Z$ , or  $(CH_2)_n-O-(CH_2)_m-CH_3$ ;

wherein  $R_{18}$  is straight chained or branched  $C_1$ - $C_6$  alkyl, -  
 15  $(CH_2)_m-Z$ , or  $(CH_2)_q-O-(CH_2)_m-CH_3$ ;

wherein each  $R_{19}$  is independently H, or straight chained or branched  $C_1$ - $C_6$  alkyl;

wherein each  $R_{20}$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl or  $C_5$ - $C_7$  cycloalkenyl; -F, -Cl, -Br, or -I; -  
 25  $NO_2$ ;  $-N_3$ ; -CN;  $-OR_{21}$ ,  $-OCOR_{21}$ ,  $-COR_{21}$ ,  $-NCOR_{21}$ ,  $-N(R_{21})_2$ ,  $-CON(R_{21})_2$ , or  $-COOR_{21}$ ; aryl or heteroaryl; or two  $R_{20}$  groups present on adjacent carbon atoms can join together to  
 30 form a methylenedioxy group;

wherein each  $R_{21}$  is independently -H; straight chained or



branched C<sub>1</sub>-C<sub>7</sub> alkyl, monofluoroalkyl or polyfluoroalkyl;  
 straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl or alkynyl; C<sub>3</sub>-  
 C<sub>7</sub> cycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, aryl or aryl(C<sub>1</sub>-  
 C<sub>6</sub>)alkyl;

5

wherein each R<sub>22</sub> is independently H, F, Cl or C<sub>1</sub>-C<sub>4</sub>  
 straight chained or branched alkyl;

wherein each m is an integer from 0 to 4 inclusive;

10

wherein each n is an integer from 1 to 4 inclusive;

wherein p is an integer from 0 to 2 inclusive;

15

wherein q is an integer from 2 to 4 inclusive;

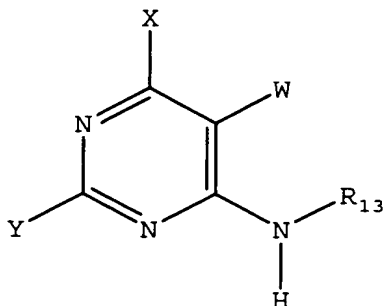
wherein t is 1 or 2; or

a pharmaceutically acceptable salt thereof.

20

The present invention provides a method of treating a  
 subject suffering from depression which comprises  
 administering to the subject an amount of compound  
 effective to treat the subject's depression wherein the  
 compound has the structure:

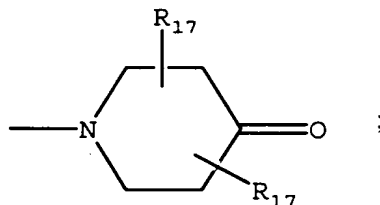
25



wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

5

wherein X is  $N(CH_3)_2$  or



10 wherein  $R_{13}$  is a bicyclic alkyl ring system, aryl or aryl( $C_1$ - $C_6$ )alkyl;

wherein Y is  $NR_{14}R_{15}$ ;

15 wherein  $R_{14}$  is H, straight chained or branched  $C_1$ - $C_6$  alkyl,  $(CH_2)_q-O-(CH_2)_m-CH_3$ ,  $C_3$ - $C_6$  cycloalkyl, or  $(C(R_{19})_2)_m-Z$ ;

wherein  $R_{15}$  is  $(C(R_{19})_2)_m-N(R_{16})_2$ ;

20 wherein Z is  $C_3$ - $C_{10}$  cycloalkyl, aryl, or heteroaryl;

wherein  $R_{16}$  is straight chained or branched  $C_1$ - $C_7$  alkyl, straight chained or branched  $C_1$ - $C_7$  monofluoroalkyl, straight chained or branched  $C_1$ - $C_7$  polyfluoroalkyl, 25 straight chained or branched  $C_2$ - $C_7$  alkenyl, straight chained or branched  $C_2$ - $C_7$  alkynyl,  $C_5$ - $C_7$  cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_q-O-(CH_2)_m-CH_3$ ;

wherein each  $R_{17}$  is independently H;  $-OR_{21}$ ,  $-OCOR_{21}$ ,  $-COR_{21}$ ,

-NCOR<sub>21</sub>, -N(R<sub>21</sub>)<sub>2</sub>, -CON(R<sub>21</sub>)<sub>2</sub>, -COOR<sub>21</sub>, straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> monofluoroalkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> polyfluoroalkyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkynyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, -(CH<sub>2</sub>)<sub>m</sub>-Z, or (CH<sub>2</sub>)<sub>n</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-CH<sub>3</sub>;

wherein each R<sub>19</sub> is independently H, or straight chained or branched C<sub>1</sub>-C<sub>6</sub> alkyl;

wherein each R<sub>21</sub> is independently -H; straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl or alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, aryl or aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl;

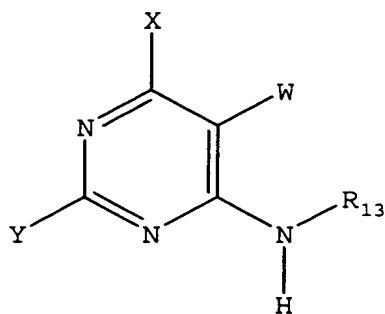
wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

wherein q is an integer from 2 to 4 inclusive; or

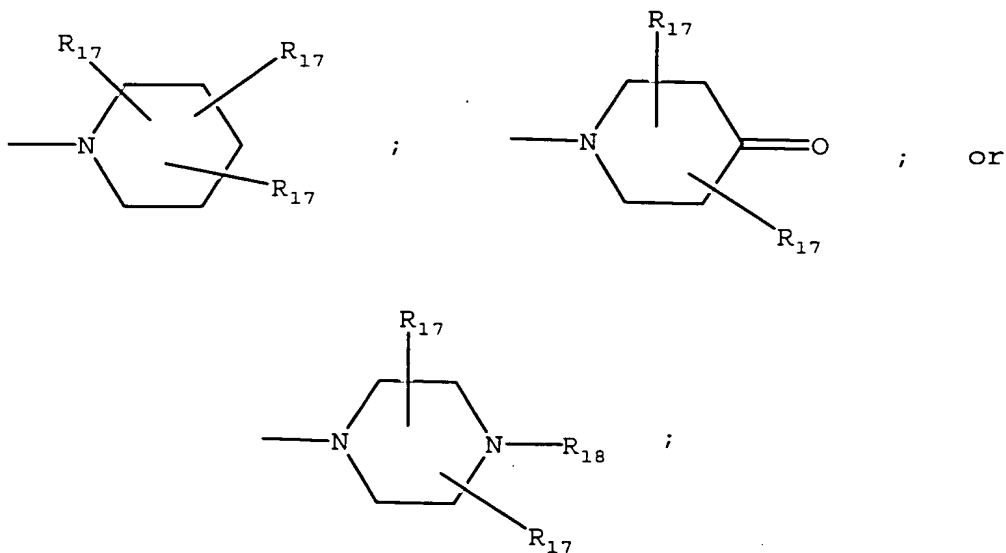
a pharmaceutically acceptable salt thereof.

The present invention also provides a method of treating a subject suffering from anxiety which comprises administering to the subject an amount of compound effective to treat the subject's anxiety wherein the compound has the structure:



wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

5 wherein X is;  $\text{NR}_{11}\text{R}_{12}$ ;



wherein  $\text{R}_{11}$  is H, straight chained or branched  $\text{C}_1\text{-C}_7$  alkyl,  $(\text{CH}_2)_q\text{-O-(CH}_2)_m\text{-CH}_3$ , aryl, or aryl  $(\text{C}_1\text{-C}_6)$  alkyl;

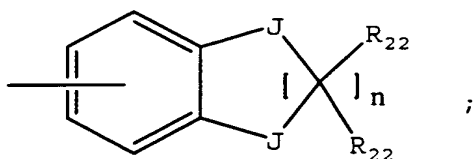
10 wherein  $\text{R}_{12}$  is straight chained or branched  $\text{C}_1\text{-C}_7$  alkyl,  $(\text{CH}_2)_q\text{-O-(CH}_2)_m\text{-CH}_3$ , or  $-(\text{CH}_2)_m\text{-Z}$ ;

wherein  $\text{R}_{13}$  is a bicyclic alkyl ring system, adamantyl, noradamantyl,  $\text{C}_3\text{-C}_{10}$  cycloalkyl, heteroaryl, aryl, aryl  $(\text{C}_1\text{-$

$C_6$  alkyl,  $Q_1$  or  $Q_2$ ;

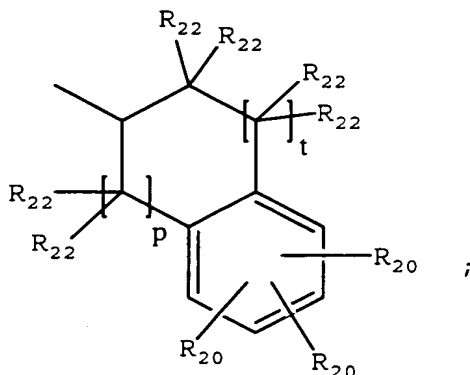
wherein aryl may be substituted with one or more  $C_1$ - $C_{10}$  straight chained or branched alkyl, aryl, heteroaryl, or  
 5  $N(R_{19})-Z$ ;

wherein  $Q_1$  is



10

wherein  $Q_2$  is

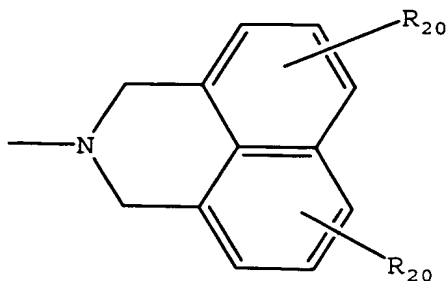
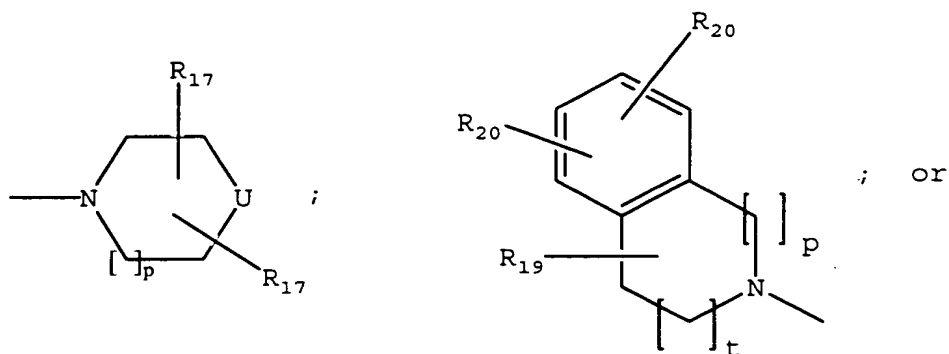


15

wherein each J is independently O, S,  $C(R_{22})_2$  or  $NR_4$ ;

wherein  $R_4$  is H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$   
 20 cycloalkenyl or aryl;

wherein Y is  $NR_{14}R_{15}$ ;



5

wherein R<sub>14</sub> is H, straight chained or branched C<sub>1</sub>-C<sub>6</sub> alkyl, (CH<sub>2</sub>)<sub>q</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-CH<sub>3</sub>, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, or (C(R<sub>19</sub>)<sub>2</sub>)<sub>m</sub>-Z;

10 wherein R<sub>15</sub> is straight chained or branched C<sub>3</sub>-C<sub>6</sub> alkyl, (CH<sub>2</sub>)<sub>q</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-CH<sub>3</sub>, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, (C(R<sub>19</sub>)<sub>2</sub>)<sub>m</sub>N(R<sub>16</sub>)<sub>2</sub> or (C(R<sub>19</sub>)<sub>2</sub>)<sub>m</sub>-Z;

15 wherein R<sub>16</sub> is straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> monofluoroalkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> polyfluoroalkyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkynyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, - (CH<sub>2</sub>)<sub>m</sub>-Z, or (CH<sub>2</sub>)<sub>q</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-CH<sub>3</sub>;

20 wherein each R<sub>17</sub> is independently H; -OR<sub>21</sub>, -OCOR<sub>21</sub>, -COR<sub>21</sub>,

-NCOR<sub>21</sub>, -N(R<sub>21</sub>)<sub>2</sub>, -CON(R<sub>21</sub>)<sub>2</sub>, -COOR<sub>21</sub>, straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> monofluoroalkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> polyfluoroalkyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkynyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, -(CH<sub>2</sub>)<sub>m</sub>-Z, or (CH<sub>2</sub>)<sub>n</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-CH<sub>3</sub>;

wherein R<sub>18</sub> is straight chained or branched C<sub>1</sub>-C<sub>6</sub> alkyl, -(CH<sub>2</sub>)<sub>m</sub>-Z, or (CH<sub>2</sub>)<sub>q</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-CH<sub>3</sub>;

wherein each R<sub>19</sub> is independently H, or straight chained or branched C<sub>1</sub>-C<sub>6</sub> alkyl;

wherein each R<sub>20</sub> is independently -H; straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl or alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl or C<sub>5</sub>-C<sub>7</sub> cycloalkenyl; -F, -Cl, -Br, or -I; -NO<sub>2</sub>; -N<sub>3</sub>; -CN; -OR<sub>21</sub>, -OCOR<sub>21</sub>, -COR<sub>21</sub>, -NCOR<sub>21</sub>, -N(R<sub>21</sub>)<sub>2</sub>, -CON(R<sub>21</sub>)<sub>2</sub>, or -COOR<sub>21</sub>; aryl or heteroaryl; or two R<sub>20</sub> groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each R<sub>21</sub> is independently -H; straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl or alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, aryl, or aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl;

wherein each R<sub>22</sub> is independently H, F, Cl or C<sub>1</sub>-C<sub>4</sub> straight chained or branched alkyl;

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

wherein p is an integer from 0 to 2 inclusive;

5

wherein q is an integer from 2 to 4 inclusive;

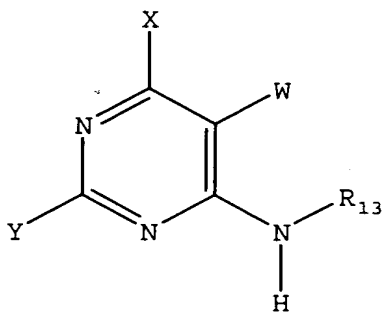
wherein t is 1 or 2;

10 wherein U is O,  $-NR_{16}$ , S,  $C(R_{17})_2$ , or  $-NSO_2R_{16}$ ;

wherein Z is  $C_3$ - $C_{10}$  cycloalkyl,  $C_4$ - $C_7$  cyclic ether,  $C_4$ - $C_7$  cyclic thioether, aryl, or heteroaryl; or

15 a pharmaceutically acceptable salt thereof.

The invention provides a method of treating a subject suffering from anxiety which comprises administering to  
20 the subject an amount of compound effective to treat the subject's anxiety wherein the compound has the structure:

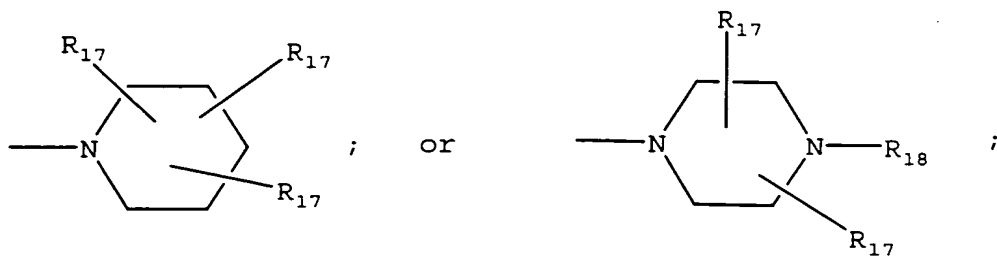


wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

25



wherein X is  $\text{NR}_{11}\text{R}_{12}$ ;



wherein  $\text{R}_{11}$  is H, straight chained or branched  $\text{C}_1\text{-C}_7$  alkyl,  $(\text{CH}_2)_q\text{-O-(CH}_2)_m\text{-CH}_3$ , aryl or aryl( $\text{C}_1\text{-C}_6$ )alkyl;

5

wherein  $\text{R}_{12}$  is straight chained or branched  $\text{C}_1\text{-C}_7$  alkyl,  $(\text{CH}_2)_q\text{-O-(CH}_2)_m\text{-CH}_3$ , or  $\text{-(CH}_2)_m\text{-Z}$ ;

wherein  $\text{R}_{13}$  is a bicyclic alkyl ring system, aryl or  
 10 aryl( $\text{C}_1\text{-C}_6$ )alkyl;

wherein Y is  $\text{NR}_{14}\text{R}_{15}$ ;



5

10

15

wherein  $R_{16}$  is straight chained or branched  $C_1$ - $C_7$  alkyl, straight chained or branched  $C_1$ - $C_7$  monofluoroalkyl, straight chained or branched  $C_1$ - $C_7$  polyfluoroalkyl, straight chained or branched  $C_2$ - $C_7$  alkenyl, straight chained or branched  $C_2$ - $C_7$  alkynyl,  $C_5$ - $C_7$  cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_q-O-(CH_2)_m-CH_3$ ;

wherein each  $R_{17}$  is independently H;  $-OR_{21}$ ,  $-OCOR_{21}$ ,  $-COR_{21}$ ,  $-NCOR_{21}$ ,  $-N(R_{21})_2$ ,  $-CON(R_{21})_2$ ,  $-COOR_{21}$ , straight chained or branched  $C_1$ - $C_7$  alkyl, straight chained or branched  $C_1$ - $C_7$  monofluoroalkyl, straight chained or branched  $C_1$ - $C_7$  polyfluoroalkyl, straight chained or branched  $C_2$ - $C_7$  alkenyl, straight chained or branched  $C_2$ - $C_7$  alkynyl,  $C_5$ - $C_7$  cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_n-O-(CH_2)_m-CH_3$ ;

wherein  $R_{18}$  is straight chained or branched  $C_1$ - $C_6$  alkyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_q-O-(CH_2)_m-CH_3$ ;

wherein each  $R_{19}$  is independently H, or straight chained or branched  $C_1$ - $C_6$  alkyl;

wherein each  $R_{20}$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl or  $C_5$ - $C_7$  cycloalkenyl; -F, -Cl, -Br, or -I;  $-NO_2$ ;  $-N_3$ ; -CN;  $-OR_{21}$ ,  $-OCOR_{21}$ ,  $-COR_{21}$ ,  $-NCOR_{21}$ ,  $-N(R_{21})_2$ ,  $-CON(R_{21})_2$ , or  $-COOR_{21}$ ; aryl or heteroaryl; or two  $R_{20}$  groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each  $R_{21}$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$  cycloalkenyl, aryl or aryl( $C_1$ - $C_6$ )alkyl;

wherein each  $m$  is an integer from 0 to 4 inclusive;

wherein each  $n$  is an integer from 1 to 4 inclusive;

wherein p is an integer from 0 to 2 inclusive;

wherein q is an integer from 2 to 4 inclusive;

5

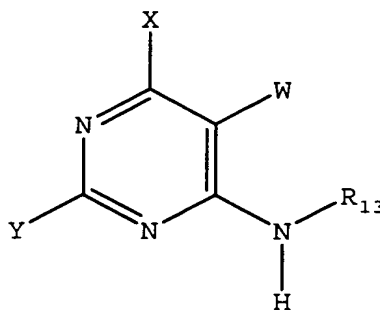
wherein t is 1 or 2; or

a pharmaceutically acceptable salt thereof.

10

The invention provides a method of treating a subject suffering from anxiety which comprises administering to the subject an amount of compound effective to treat the subject's anxiety wherein the compound has the structure:

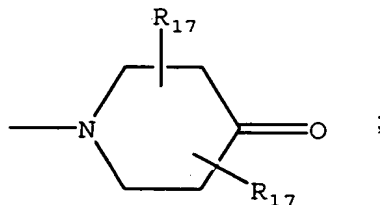
15



wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

20

wherein X is  $N(CH_3)_2$  or

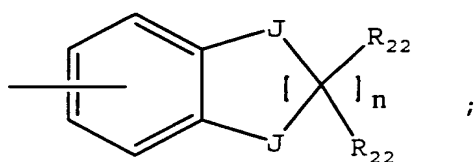


wherein  $R_{13}$  is an aryl, adamantyl, noradamantyl,  $C_3$ - $C_{10}$  cycloalkyl, heteroaryl,  $Q_1$  or  $Q_2$ ;

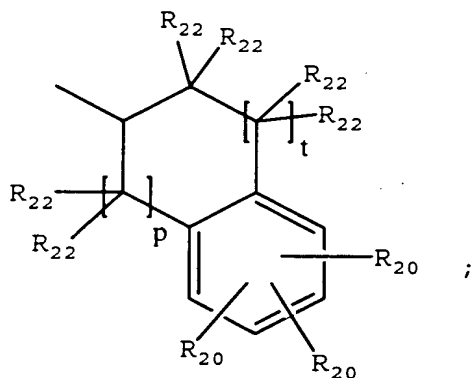
5 wherein aryl may be substituted with one or more  $C_1$ - $C_{10}$  straight chained or branched alkyl, aryl, heteroaryl, or  $N(R_{19})-Z$ ;

wherein  $Q_1$  is

10



wherein  $Q_2$  is

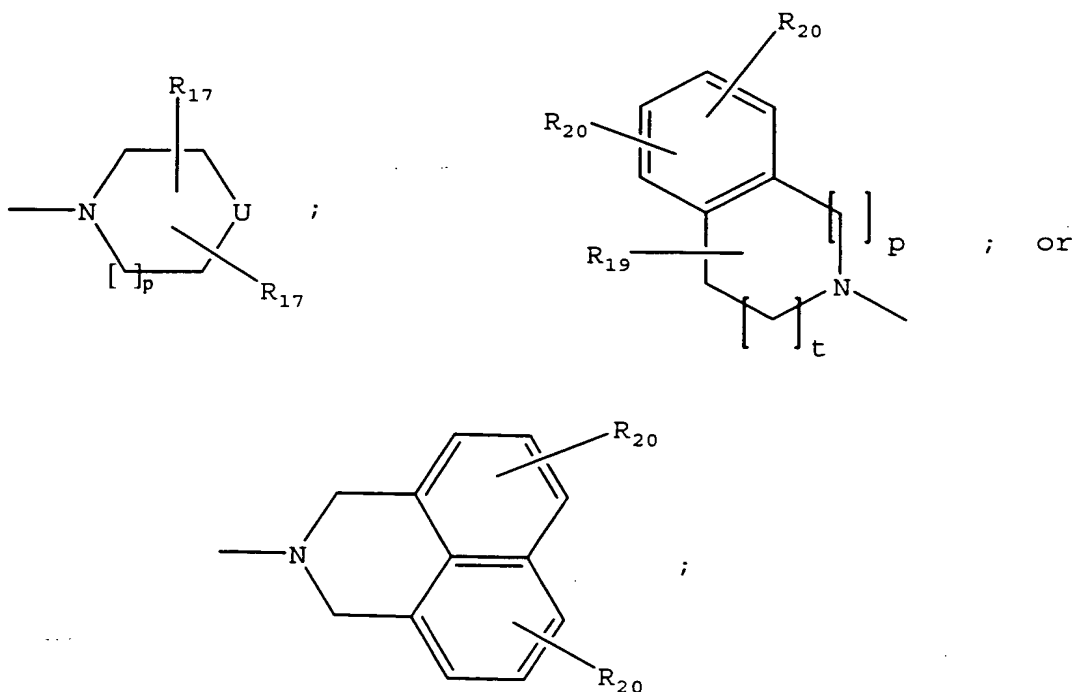


15

wherein each  $J$  is independently  $O$ ,  $S$ ,  $C(R_{22})_2$  or  $NR_4$ ;

20 wherein  $R_4$  is  $-H$ ; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$  cycloalkenyl or aryl;

wherein Y is  $\text{NR}_{14}\text{R}_{15}$ ;



5

wherein  $\text{R}_{14}$  is H, straight chained or branched  $\text{C}_1$ - $\text{C}_6$  alkyl,  $(\text{CH}_2)_q\text{-O-}(\text{CH}_2)_m\text{-CH}_3$ ,  $\text{C}_3$ - $\text{C}_6$  cycloalkyl, or  $(\text{C}(\text{R}_{19})_2)_m\text{-Z}$ ;

10 wherein  $\text{R}_{15}$  is straight chained or branched  $\text{C}_3$ - $\text{C}_6$  alkyl,  $(\text{CH}_2)_q\text{-O-}(\text{CH}_2)_m\text{-CH}_3$ ,  $\text{C}_3$ - $\text{C}_6$  cycloalkyl, or  $(\text{C}(\text{R}_{19})_2)_m\text{-Z}$ ;

wherein U is O,  $\text{-NR}_{16}$ , S,  $\text{C}(\text{R}_{17})_2$ , or  $\text{-NSO}_2\text{R}_{16}$ ;

wherein Z is  $\text{C}_3$ - $\text{C}_{10}$  cycloalkyl, aryl, or heteroaryl;

15

wherein  $\text{R}_{16}$  is straight chained or branched  $\text{C}_1$ - $\text{C}_7$  alkyl, straight chained or branched  $\text{C}_1$ - $\text{C}_7$  monofluoroalkyl, straight chained or branched  $\text{C}_1$ - $\text{C}_7$  polyfluoroalkyl,

straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkynyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, - (CH<sub>2</sub>)<sub>m</sub>-Z, or (CH<sub>2</sub>)<sub>q</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-CH<sub>3</sub>;

5 wherein each R<sub>17</sub> is independently H; -OR<sub>21</sub>, -OCOR<sub>21</sub>, -COR<sub>21</sub>, -NCOR<sub>21</sub>, -N(R<sub>21</sub>)<sub>2</sub>, -CON(R<sub>21</sub>)<sub>2</sub>, -COOR<sub>21</sub>, straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> monofluoroalkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> polyfluoroalkyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkynyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, - (CH<sub>2</sub>)<sub>m</sub>-Z, or (CH<sub>2</sub>)<sub>n</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-CH<sub>3</sub>;

wherein R<sub>18</sub> is straight chained or branched C<sub>1</sub>-C<sub>6</sub> alkyl, - (CH<sub>2</sub>)<sub>m</sub>-Z, or (CH<sub>2</sub>)<sub>q</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-CH<sub>3</sub>;

15 wherein each R<sub>19</sub> is independently H, or straight chained or branched C<sub>1</sub>-C<sub>6</sub> alkyl;

wherein each R<sub>20</sub> is independently -H; straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl or alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl or C<sub>5</sub>-C<sub>7</sub> cycloalkenyl; -F, -Cl, -Br, or -I; -NO<sub>2</sub>; -N<sub>3</sub>; -CN; -OR<sub>21</sub>, -OCOR<sub>21</sub>, -COR<sub>21</sub>, -NCOR<sub>21</sub>, -N(R<sub>21</sub>)<sub>2</sub>, -CON(R<sub>21</sub>)<sub>2</sub>, or -COOR<sub>21</sub>; aryl or heteroaryl; or two R<sub>20</sub> groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each R<sub>21</sub> is independently -H; straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl or alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, aryl or aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl;

wherein each  $R_{22}$  is independently H, F, Cl or  $C_1-C_4$  straight chained or branched alkyl;

wherein each m is an integer from 0 to 4 inclusive;

5

wherein each n is an integer from 1 to 4 inclusive;

wherein p is an integer from 0 to 2 inclusive;

10

wherein q is an integer from 2 to 4 inclusive;

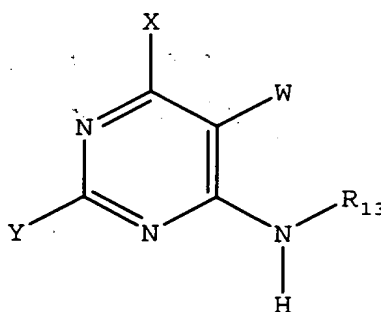
wherein t is 1 or 2; or

a pharmaceutically acceptable salt thereof.

15

The invention provides a method of treating a subject suffering from anxiety which comprises administering to the subject an amount of compound effective to treat the subject's anxiety wherein the compound has the structure:

20

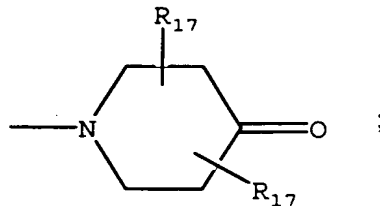


wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

25

wherein X is  $N(CH_3)_2$  or





wherein  $R_{13}$  is a bicyclic alkyl ring system, aryl or  
 5 aryl( $C_1$ - $C_6$ )alkyl;

wherein Y is  $NR_{14}R_{15}$ ;

wherein  $R_{14}$  is H, straight chained or branched  $C_1$ - $C_6$  alkyl,  
 10  $(CH_2)_q-O-(CH_2)_m-CH_3$ ,  $C_3$ - $C_6$  cycloalkyl, or  $(C(R_{19})_2)_m-Z$ ;

wherein  $R_{15}$  is  $(C(R_{19})_2)_m-N(R_{16})_2$ ;

wherein Z is  $C_3$ - $C_{10}$  cycloalkyl, aryl, or heteroaryl;

15 wherein  $R_{16}$  is straight chained or branched  $C_1$ - $C_7$  alkyl,  
 straight chained or branched  $C_1$ - $C_7$  monofluoroalkyl,  
 straight chained or branched  $C_1$ - $C_7$  polyfluoroalkyl,  
 straight chained or branched  $C_2$ - $C_7$  alkenyl, straight  
 20 chained or branched  $C_2$ - $C_7$  alkynyl,  $C_5$ - $C_7$  cycloalkenyl, -  
 $(CH_2)_m-Z$ , or  $(CH_2)_q-O-(CH_2)_m-CH_3$ ;

wherein each  $R_{17}$  is independently H;  $-OR_{21}$ ,  $-OCOR_{21}$ ,  $-COR_{21}$ ,  
 $-NCOR_{21}$ ,  $-N(R_{21})_2$ ,  $-CON(R_{21})_2$ ,  $-COOR_{21}$ , straight chained or  
 25 branched  $C_1$ - $C_7$  alkyl, straight chained or branched  $C_1$ - $C_7$   
 monofluoroalkyl, straight chained or branched  $C_1$ - $C_7$   
 polyfluoroalkyl, straight chained or branched  $C_2$ - $C_7$   
 alkenyl, straight chained or branched  $C_2$ - $C_7$  alkynyl,  $C_5$ - $C_7$   
 cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_n-O-(CH_2)_m-CH_3$ ;

wherein each  $R_{19}$  is independently H, or straight chained or branched  $C_1-C_6$  alkyl;

5 wherein each  $R_{21}$  is independently -H; straight chained or branched  $C_1-C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2-C_7$  alkenyl or alkynyl;  $C_3-C_7$  cycloalkyl,  $C_5-C_7$  cycloalkenyl, aryl or aryl( $C_1-C_6$ )alkyl;

10

wherein each m is an integer from 0 to 4 inclusive;

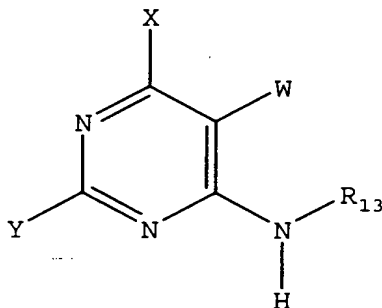
wherein each n is an integer from 1 to 4 inclusive;

15

wherein q is an integer from 2 to 4 inclusive; or

a pharmaceutically acceptable salt thereof.

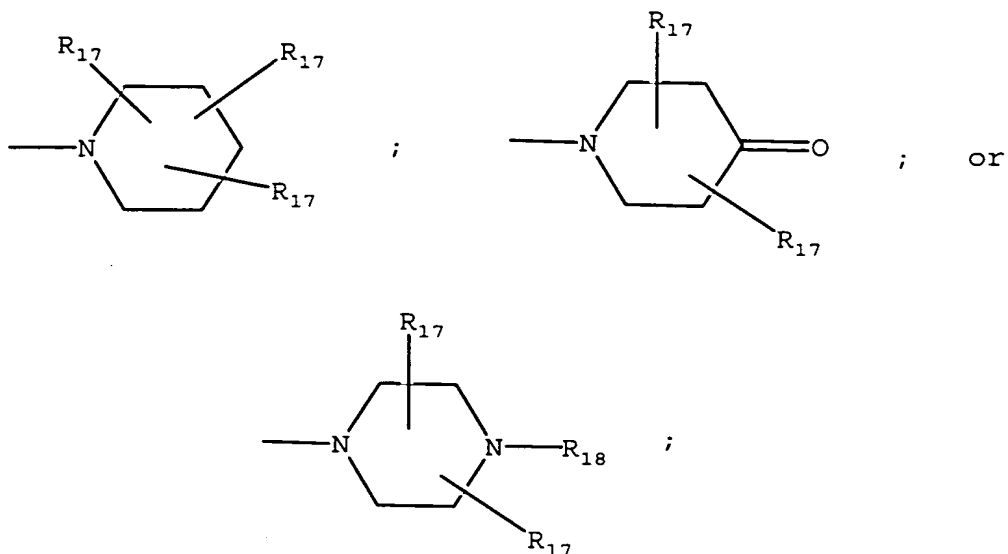
The invention also provides a pharmaceutical composition  
 20 comprising a pharmaceutically acceptable carrier and a compound having the structure:



wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

25

wherein X is;  $\text{NR}_{11}\text{R}_{12}$ ;



wherein  $\text{R}_{11}$  is H, straight chained or branched  $\text{C}_1\text{-C}_7$  alkyl,  $(\text{CH}_2)_q\text{-O-}(\text{CH}_2)_m\text{-CH}_3$ , aryl, or aryl  $(\text{C}_1\text{-C}_6)$  alkyl;

5

wherein  $\text{R}_{12}$  is straight chained or branched  $\text{C}_1\text{-C}_7$  alkyl,  $(\text{CH}_2)_q\text{-O-}(\text{CH}_2)_m\text{-CH}_3$ , or  $-(\text{CH}_2)_m\text{-Z}$ ;

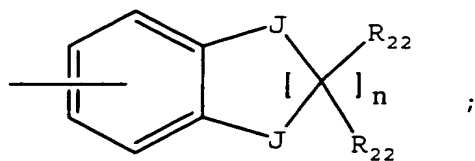
wherein  $\text{R}_{13}$  is a bicyclic alkyl ring system, adamantyl, noradamantyl,  $\text{C}_3\text{-C}_{10}$  cycloalkyl, heteroaryl, aryl, aryl  $(\text{C}_1\text{-C}_6)$  alkyl,  $\text{Q}_1$  or  $\text{Q}_2$ ;

10

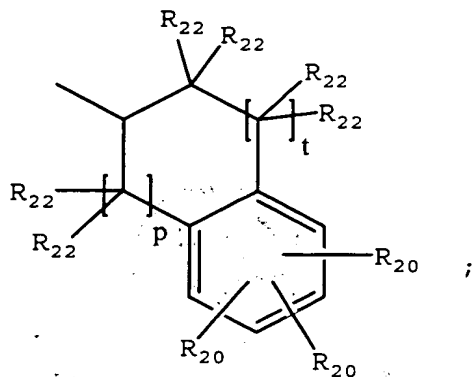
wherein aryl may be substituted with one or more  $\text{C}_1\text{-C}_{10}$  straight chained or branched alkyl, aryl, heteroaryl, or  $\text{N}(\text{R}_{19})\text{-Z}$ ;

15

wherein  $\text{Q}_1$  is



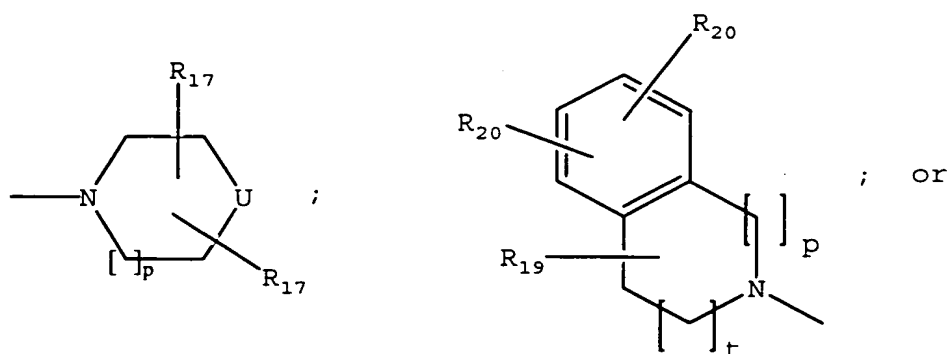
wherein  $Q_2$  is



wherein each J is independently O, S, C(R<sub>22</sub>)<sub>2</sub> or NR<sub>4</sub>;

wherein R<sub>4</sub> is H; straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl or alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl or aryl;

wherein Y is  $\text{NR}_{14}\text{R}_{15}$ ;



5

wherein  $R_{14}$  is H, straight chained or branched  $C_1$ - $C_6$  alkyl,  $(CH_2)_q-O-(CH_2)_m-CH_3$ ,  $C_3$ - $C_6$  cycloalkyl, or  $(C(R_{19})_2)_m-Z$ ;

10

wherein  $R_{15}$  is straight chained or branched  $C_3$ - $C_6$  alkyl,  $(CH_2)_q-O-(CH_2)_m-CH_3$ ,  $C_3$ - $C_6$  cycloalkyl,  $(C(R_{19})_2)_mN(R_{16})_2$  or  $(C(R_{19})_2)_m-Z$ ;

15

wherein  $R_{16}$  is straight chained or branched  $C_1$ - $C_7$  alkyl, straight chained or branched  $C_1$ - $C_7$  monofluoroalkyl, straight chained or branched  $C_1$ - $C_7$  polyfluoroalkyl, straight chained or branched  $C_2$ - $C_7$  alkenyl, straight chained or branched  $C_2$ - $C_7$  alkynyl,  $C_5$ - $C_7$  cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_q-O-(CH_2)_m-CH_3$ ;

20

wherein each  $R_{17}$  is independently H;  $-OR_{21}$ ,  $-OCOR_{21}$ ,  $-COR_{21}$ ,

-NCOR<sub>21</sub>, -N(R<sub>21</sub>)<sub>2</sub>, -CON(R<sub>21</sub>)<sub>2</sub>, -COOR<sub>21</sub>, straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> monofluoroalkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> polyfluoroalkyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkynyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, -(CH<sub>2</sub>)<sub>m</sub>-Z, or (CH<sub>2</sub>)<sub>n</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-CH<sub>3</sub>;

wherein R<sub>18</sub> is straight chained or branched C<sub>1</sub>-C<sub>6</sub> alkyl, -(CH<sub>2</sub>)<sub>m</sub>-Z, or (CH<sub>2</sub>)<sub>q</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-CH<sub>3</sub>;

wherein each R<sub>19</sub> is independently H, or straight chained or branched C<sub>1</sub>-C<sub>6</sub> alkyl;

wherein each R<sub>20</sub> is independently -H; straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl or alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl or C<sub>5</sub>-C<sub>7</sub> cycloalkenyl; -F, -Cl, -Br, or -I; -NO<sub>2</sub>; -N<sub>3</sub>; -CN; -OR<sub>21</sub>, -OCOR<sub>21</sub>, -COR<sub>21</sub>, -NCOR<sub>21</sub>, -N(R<sub>21</sub>)<sub>2</sub>, -CON(R<sub>21</sub>)<sub>2</sub>, or -COOR<sub>21</sub>; aryl or heteroaryl; or two R<sub>20</sub> groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each R<sub>21</sub> is independently -H; straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl or alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, aryl, or aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl;

wherein each R<sub>22</sub> is independently H, F, Cl or C<sub>1</sub>-C<sub>4</sub> straight chained or branched alkyl;

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

wherein p is an integer from 0 to 2 inclusive;

5

wherein q is an integer from 2 to 4 inclusive;

wherein t is 1 or 2;

10

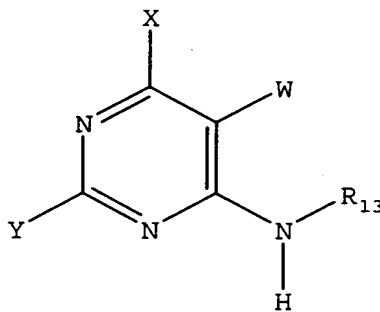
wherein U is O,  $-NR_{16}$ , S,  $C(R_{17})_2$ , or  $-NSO_2R_{16}$ ;

wherein Z is  $C_3-C_{10}$  cycloalkyl,  $C_4-C_7$  cyclic ether,  $C_4-C_7$  cyclic thioether, aryl, or heteroaryl; or

15

a pharmaceutically acceptable salt thereof.

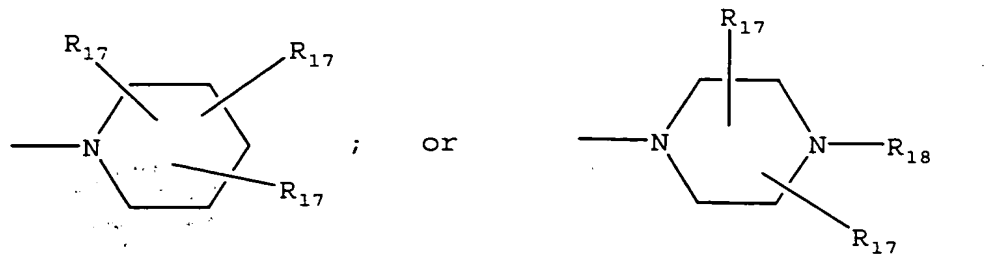
The invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a  
20 compound having the structure:



wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

25

wherein X is  $\text{NR}_{11}\text{R}_{12}$ ;



wherein  $\text{R}_{11}$  is H, straight chained or branched  $\text{C}_1\text{-C}_7$  alkyl,  $(\text{CH}_2)_q\text{-O-(CH}_2)_m\text{-CH}_3$ , aryl or aryl( $\text{C}_1\text{-C}_6$ )alkyl;

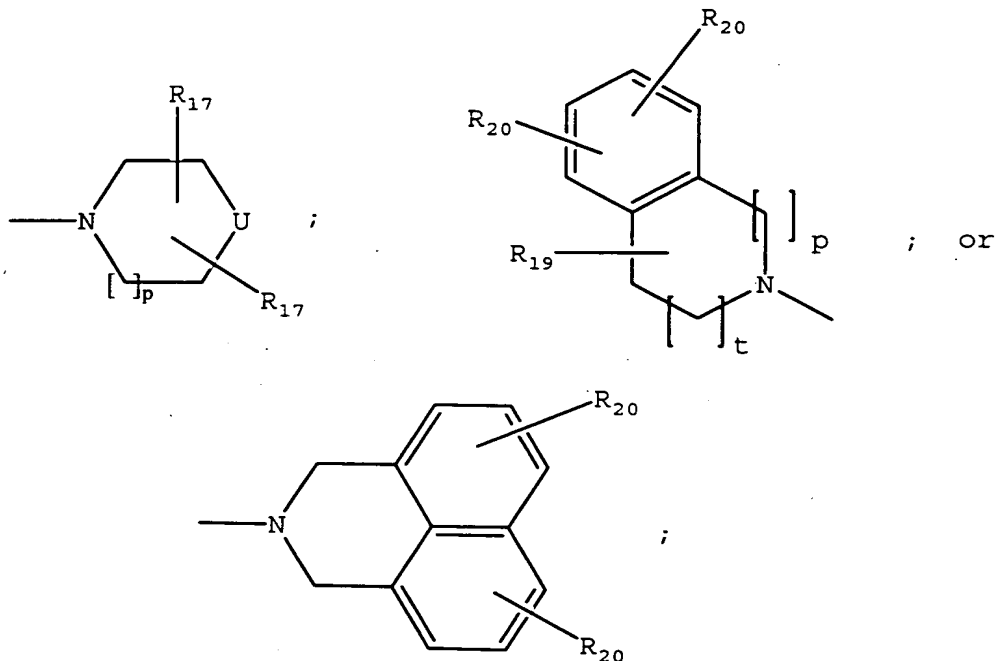
5

wherein  $\text{R}_{12}$  is straight chained or branched  $\text{C}_1\text{-C}_7$  alkyl,  $(\text{CH}_2)_q\text{-O-(CH}_2)_m\text{-CH}_3$ , or  $\text{-(CH}_2)_m\text{-Z}$ ;

wherein  $\text{R}_{13}$  is a bicyclic alkyl ring system, aryl or  
 10 aryl( $\text{C}_1\text{-C}_6$ )alkyl;

wherein Y is  $\text{NR}_{14}\text{R}_{15}$ ;





wherein  $R_{14}$  is H, straight chained or branched  $C_1$ - $C_6$  alkyl,  $(CH_2)_q$ -O- $(CH_2)_m$ - $CH_3$ ,  $C_3$ - $C_6$  cycloalkyl, or  $(C(R_{19})_2)_m$ -Z;

5

wherein  $R_{15}$  is straight chained or branched  $C_3$ - $C_6$  alkyl,  $(CH_2)_q$ -O- $(CH_2)_m$ - $CH_3$ ,  $C_3$ - $C_6$  cycloalkyl, or  $(C(R_{19})_2)_m$ -Z;

wherein U is O,  $-NR_{16}$ , S,  $C(R_{17})_2$ , or  $-NSO_2R_{16}$ ;

10

wherein Z is  $C_3$ - $C_{10}$  cycloalkyl, aryl, or heteroaryl;

wherein  $R_{16}$  is straight chained or branched  $C_1$ - $C_7$  alkyl, straight chained or branched  $C_1$ - $C_7$  monofluoroalkyl, straight chained or branched  $C_1$ - $C_7$  polyfluoroalkyl, straight chained or branched  $C_2$ - $C_7$  alkenyl, straight chained or branched  $C_2$ - $C_7$  alkynyl,  $C_5$ - $C_7$  cycloalkenyl,  $-(CH_2)_m$ -Z, or  $(CH_2)_q$ -O- $(CH_2)_m$ - $CH_3$ ;

15

wherein each  $R_{17}$  is independently H;  $-OR_{21}$ ,  $-OCOR_{21}$ ,  $-COR_{21}$ ,  $-NCOR_{21}$ ,  $-N(R_{21})_2$ ,  $-CON(R_{21})_2$ ,  $-COOR_{21}$ , straight chained or branched  $C_1$ - $C_7$  alkyl, straight chained or branched  $C_1$ - $C_7$  monofluoroalkyl, straight chained or branched  $C_1$ - $C_7$  polyfluoroalkyl, straight chained or branched  $C_2$ - $C_7$  alkenyl, straight chained or branched  $C_2$ - $C_7$  alkynyl,  $C_5$ - $C_7$  cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_n-O-(CH_2)_m-CH_3$ ;

wherein  $R_{18}$  is straight chained or branched  $C_1$ - $C_6$  alkyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_q-O-(CH_2)_m-CH_3$ ;

wherein each  $R_{19}$  is independently H, or straight chained or branched  $C_1$ - $C_6$  alkyl;

wherein each  $R_{20}$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl or  $C_5$ - $C_7$  cycloalkenyl; -F, -Cl, -Br, or -I;  $-NO_2$ ;  $-N_3$ ; -CN;  $-OR_{21}$ ,  $-OCOR_{21}$ ,  $-COR_{21}$ ,  $-NCOR_{21}$ ,  $-N(R_{21})_2$ ,  $-CON(R_{21})_2$ , or  $-COOR_{21}$ ; aryl or heteroaryl; or two  $R_{20}$  groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each  $R_{21}$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$  cycloalkenyl, aryl or aryl( $C_1$ - $C_6$ )alkyl;

wherein each  $m$  is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

wherein p is an integer from 0 to 2 inclusive;

5

wherein q is an integer from 2 to 4 inclusive;

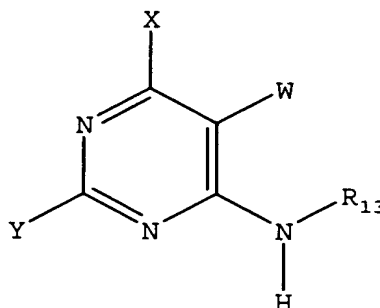
wherein t is 1 or 2; or

10

a pharmaceutically acceptable salt thereof.

The invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound having the structure:

15

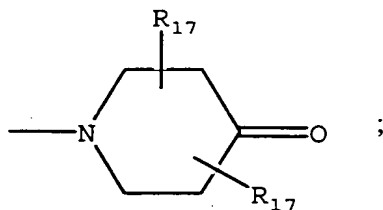


20

wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

wherein X is N(CH<sub>3</sub>)<sub>2</sub> or

25



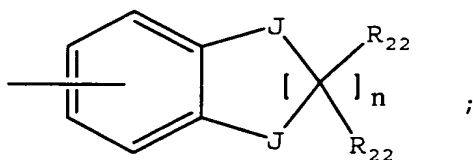
wherein  $R_{13}$  is an aryl, adamantyl, noradamantyl,  $C_3$ - $C_{10}$  cycloalkyl, heteroaryl,  $Q_1$  or  $Q_2$ ;

5

wherein aryl may be substituted with one or more  $C_1$ - $C_{10}$  straight chained or branched alkyl, aryl, heteroaryl, or  $N(R_{19})-Z$ ;

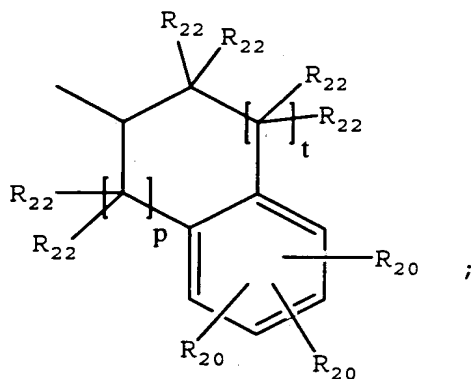
10

wherein  $Q_1$  is



wherein  $Q_2$  is

15

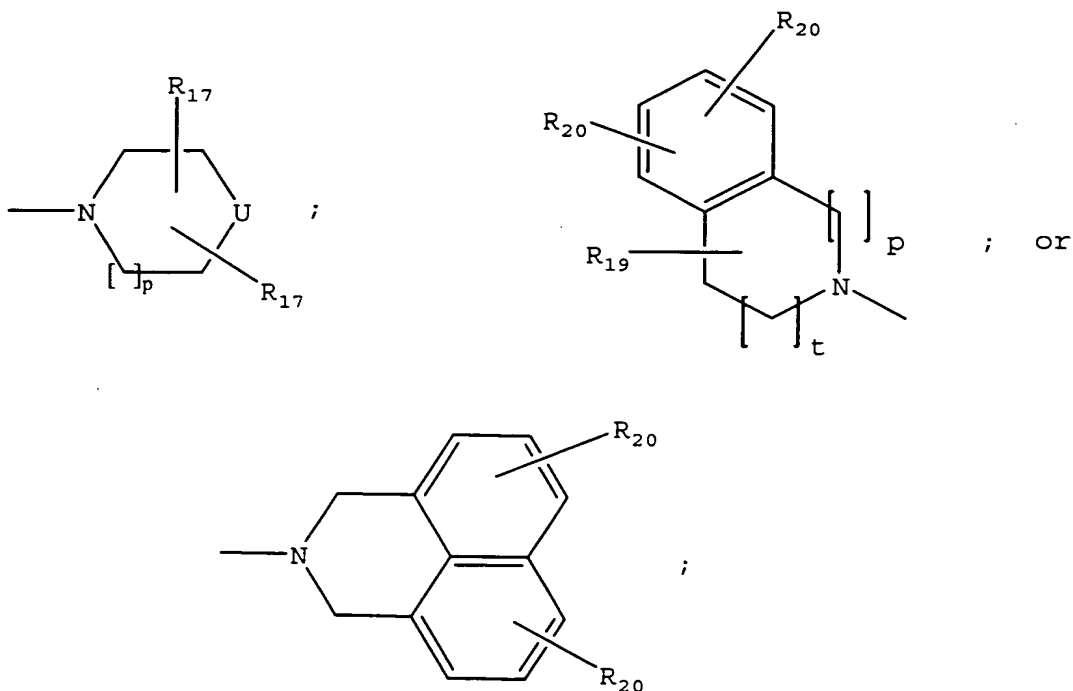


wherein each  $J$  is independently  $O$ ,  $S$ ,  $C(R_{22})_2$  or  $NR_4$ ;

wherein  $R_4$  is -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$  cycloalkenyl or aryl;

5

wherein Y is  $NR_{14}R_{15}$ ;



10 wherein  $R_{14}$  is H, straight chained or branched  $C_1$ - $C_6$  alkyl,  $(CH_2)_q-O-(CH_2)_m-CH_3$ ,  $C_3$ - $C_6$  cycloalkyl, or  $(C(R_{19})_2)_m-Z$ ;

wherein  $R_{15}$  is straight chained or branched  $C_3$ - $C_6$  alkyl,  $(CH_2)_q-O-(CH_2)_m-CH_3$ ,  $C_3$ - $C_6$  cycloalkyl, or  $(C(R_{19})_2)_m-Z$ ;

15

wherein  $U$  is O,  $-NR_{16}$ , S,  $C(R_{17})_2$ , or  $-NSO_2R_{16}$ ;

wherein  $Z$  is  $C_3$ - $C_{10}$  cycloalkyl, aryl, or heteroaryl;

wherein  $R_{16}$  is straight chained or branched  $C_1$ - $C_7$  alkyl, straight chained or branched  $C_1$ - $C_7$  monofluoroalkyl, straight chained or branched  $C_1$ - $C_7$  polyfluoroalkyl,  
 5 straight chained or branched  $C_2$ - $C_7$  alkenyl, straight chained or branched  $C_2$ - $C_7$  alkynyl,  $C_5$ - $C_7$  cycloalkenyl, -  
 $(CH_2)_m-Z$ , or  $(CH_2)_q-O-(CH_2)_m-CH_3$ ;

wherein each  $R_{17}$  is independently H;  $-OR_{21}$ ,  $-OCOR_{21}$ ,  $-COR_{21}$ ,  
 10  $-NCOR_{21}$ ,  $-N(R_{21})_2$ ,  $-CON(R_{21})_2$ ,  $-COOR_{21}$ , straight chained or branched  $C_1$ - $C_7$  alkyl, straight chained or branched  $C_1$ - $C_7$  monofluoroalkyl, straight chained or branched  $C_1$ - $C_7$  polyfluoroalkyl, straight chained or branched  $C_2$ - $C_7$  alkenyl, straight chained or branched  $C_2$ - $C_7$  alkynyl,  $C_5$ - $C_7$   
 15 cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_n-O-(CH_2)_m-CH_3$ ;

wherein  $R_{18}$  is straight chained or branched  $C_1$ - $C_6$  alkyl, -  
 $(CH_2)_m-Z$ , or  $(CH_2)_q-O-(CH_2)_m-CH_3$ ;

20 wherein each  $R_{19}$  is independently H, or straight chained or branched  $C_1$ - $C_6$  alkyl;

wherein each  $R_{20}$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl;  
 25 straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl or  $C_5$ - $C_7$  cycloalkenyl; -F, -Cl, -Br, or -I; - $NO_2$ ; - $N_3$ ; -CN;  $-OR_{21}$ ,  $-OCOR_{21}$ ,  $-COR_{21}$ ,  $-NCOR_{21}$ ,  $-N(R_{21})_2$ , -  
 $CON(R_{21})_2$ , or  $-COOR_{21}$ ; aryl or heteroaryl; or two  $R_{20}$  groups present on adjacent carbon atoms can join together to  
 30 form a methylenedioxy group;

wherein each  $R_{21}$  is independently -H; straight chained or

branched C<sub>1</sub>-C<sub>7</sub> alkyl, monofluoroalkyl or polyfluoroalkyl;  
 straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl or alkynyl; C<sub>3</sub>-  
 C<sub>7</sub> cycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, aryl or aryl(C<sub>1</sub>-  
 C<sub>6</sub>)alkyl;

5

wherein each R<sub>22</sub> is independently H, F, Cl or C<sub>1</sub>-C<sub>4</sub>  
 straight chained or branched alkyl;

wherein each m is an integer from 0 to 4 inclusive;

10

wherein each n is an integer from 1 to 4 inclusive;

wherein p is an integer from 0 to 2 inclusive;

15

wherein q is an integer from 2 to 4 inclusive;

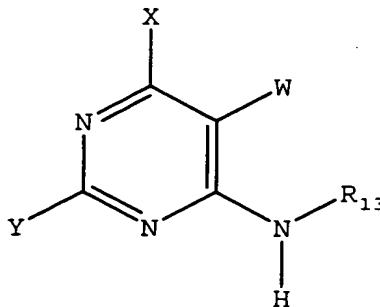
wherein t is 1 or 2; or

a pharmaceutically acceptable salt thereof.

20

The invention provides a pharmaceutical composition  
 comprising a pharmaceutically acceptable carrier and a  
 compound having the structure:

25

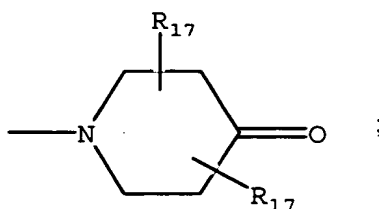


5

wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

10

wherein X is  $N(CH_3)_2$  or



15

wherein  $R_{13}$  is a bicyclic alkyl ring system, aryl or aryl( $C_1-C_6$ )alkyl;

wherein Y is  $NR_{14}R_{15}$ ;

wherein  $R_{14}$  is H, straight chained or branched  $C_1-C_6$  alkyl,  $(CH_2)_q-O-(CH_2)_m-CH_3$ ,  $C_3-C_6$  cycloalkyl, or  $(C(R_{19})_2)_m-Z$ ;

20

wherein  $R_{15}$  is  $(C(R_{19})_2)_m-N(R_{16})_2$ ;

wherein Z is  $C_3-C_{10}$  cycloalkyl, aryl, or heteroaryl;

25

wherein  $R_{16}$  is straight chained or branched  $C_1-C_7$  alkyl, straight chained or branched  $C_1-C_7$  monofluoroalkyl, straight chained or branched  $C_1-C_7$  polyfluoroalkyl, straight chained or branched  $C_2-C_7$  alkenyl, straight chained or branched  $C_2-C_7$  alkynyl,  $C_5-C_7$  cycloalkenyl, --



$(CH_2)_m-Z$ , or  $(CH_2)_q-O-(CH_2)_m-CH_3$ ;

5 wherein each  $R_{17}$  is independently H;  $-OR_{21}$ ,  $-OCOR_{21}$ ,  $-COR_{21}$ ,  
 $-NCOR_{21}$ ,  $-N(R_{21})_2$ ,  $-CON(R_{21})_2$ ,  $-COOR_{21}$ , straight chained or  
 branched  $C_1-C_7$  alkyl, straight chained or branched  $C_1-C_7$   
 monofluoroalkyl, straight chained or branched  $C_1-C_7$   
 polyfluoroalkyl, straight chained or branched  $C_2-C_7$   
 alkenyl, straight chained or branched  $C_2-C_7$  alkynyl,  $C_5-C_7$   
 cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_n-O-(CH_2)_m-CH_3$ ;

10

wherein each  $R_{19}$  is independently H, or straight chained  
 or branched  $C_1-C_6$  alkyl;

15 wherein each  $R_{21}$  is independently -H; straight chained or  
 branched  $C_1-C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl;  
 straight chained or branched  $C_2-C_7$  alkenyl or alkynyl;  $C_3-$   
 $C_7$  cycloalkyl,  $C_5-C_7$  cycloalkenyl, aryl or aryl( $C_1-$   
 $C_6$ )alkyl;

20 wherein each m is an integer from 0 to 4 inclusive;

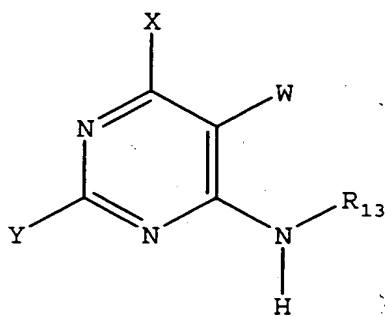
wherein each n is an integer from 1 to 4 inclusive;

wherein q is an integer from 2 to 4 inclusive; or

25

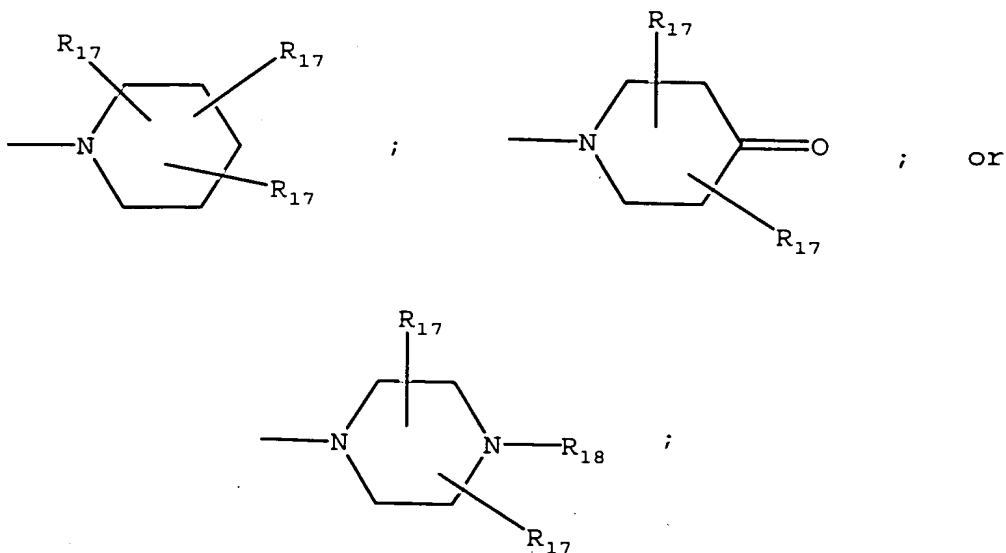
a pharmaceutically acceptable salt thereof.

The invention provides a compound having the structure:



wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

5 wherein X is;  $\text{NR}_{11}\text{R}_{12}$ ;



wherein  $\text{R}_{11}$  is H, straight chained or branched  $\text{C}_1\text{-C}_7$  alkyl,  $(\text{CH}_2)_q\text{-O-(CH}_2)_m\text{-CH}_3$ , aryl, or aryl  $(\text{C}_1\text{-C}_6)$  alkyl;

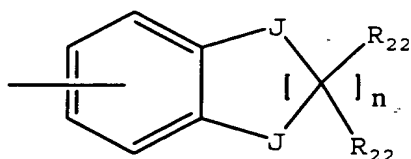
10 wherein  $\text{R}_{12}$  is straight chained or branched  $\text{C}_1\text{-C}_7$  alkyl,  $(\text{CH}_2)_q\text{-O-(CH}_2)_m\text{-CH}_3$ , or  $-(\text{CH}_2)_m\text{-Z}$ ;

wherein  $\text{R}_{13}$  is a bicyclic alkyl ring system, adamantyl, noradamantyl,  $\text{C}_3\text{-C}_{10}$  cycloalkyl, heteroaryl, aryl, aryl  $(\text{C}_1\text{-C}_6)$  alkyl;

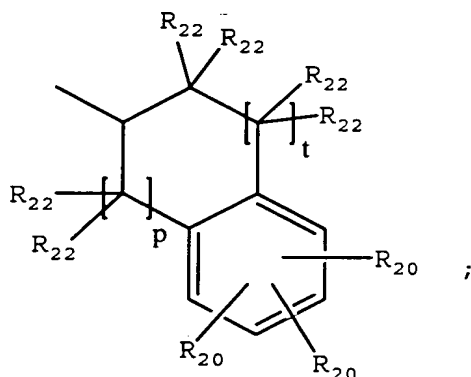
C<sub>6</sub>)alkyl, Q<sub>1</sub> or Q<sub>2</sub>;

wherein aryl may be substituted with one or more C<sub>1</sub>-C<sub>10</sub>  
 straight chained or branched alkyl, aryl, heteroaryl, or  
 5 N(R<sub>19</sub>)-Z;

wherein Q<sub>1</sub> is



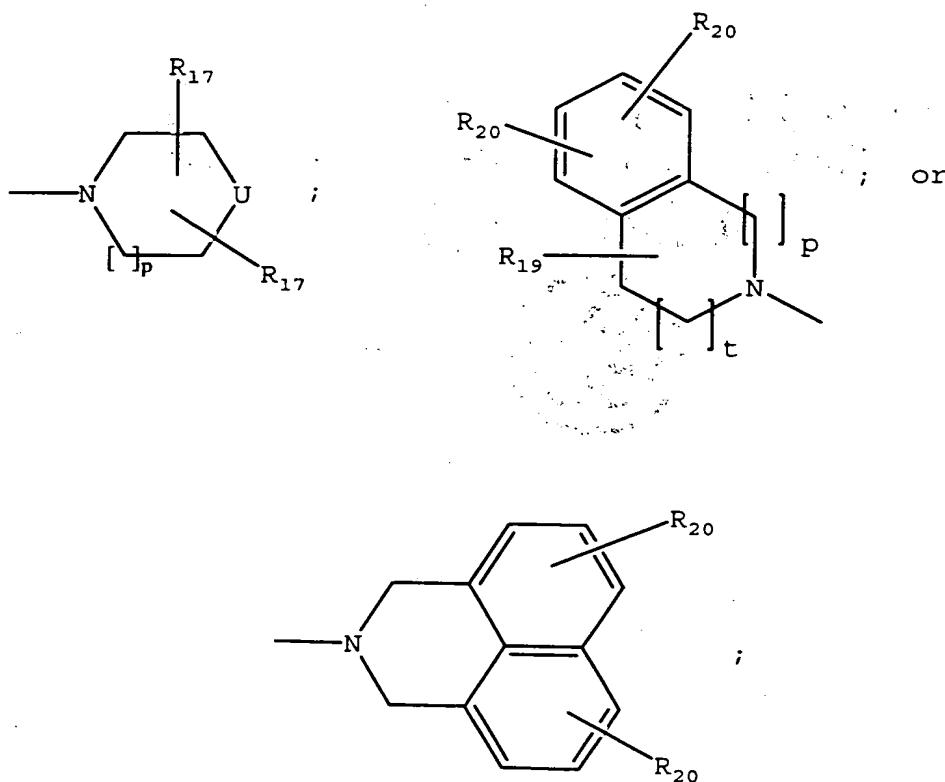
wherein Q<sub>2</sub> is



15 wherein each J is independently O, S, C(R<sub>22</sub>)<sub>2</sub> or NR<sub>4</sub>;

wherein R<sub>4</sub> is H; straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl,  
 monofluoroalkyl or polyfluoroalkyl; straight chained or  
 branched C<sub>2</sub>-C<sub>7</sub> alkenyl or alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>5</sub>-C<sub>7</sub>  
 20 cycloalkenyl or aryl;

wherein Y is NR<sub>14</sub>R<sub>15</sub>;



5

wherein  $R_{14}$  is H, straight chained or branched  $C_1$ - $C_6$  alkyl,  $(CH_2)_q-O-(CH_2)_m-CH_3$ ,  $C_3$ - $C_6$  cycloalkyl, or  $(C(R_{19})_2)_m-Z$ ;

10

wherein  $R_{15}$  is straight chained or branched  $C_3$ - $C_6$  alkyl,  $(CH_2)_q-O-(CH_2)_m-CH_3$ ,  $C_3$ - $C_6$  cycloalkyl,  $(C(R_{19})_2)_mN(R_{16})_2$  or  $(C(R_{19})_2)_m-Z$ ;

15

wherein  $R_{16}$  is straight chained or branched  $C_1$ - $C_7$  alkyl, straight chained or branched  $C_1$ - $C_7$  monofluoroalkyl, straight chained or branched  $C_1$ - $C_7$  polyfluoroalkyl, straight chained or branched  $C_2$ - $C_7$  alkenyl, straight chained or branched  $C_2$ - $C_7$  alkynyl,  $C_5$ - $C_7$  cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_q-O-(CH_2)_m-CH_3$ ;

20

wherein each  $R_{17}$  is independently H;  $-OR_{21}$ ,  $-OCOR_{21}$ ,  $-COR_{21}$ ,

-NCOR<sub>21</sub>, -N(R<sub>21</sub>)<sub>2</sub>, -CON(R<sub>21</sub>)<sub>2</sub>, -COOR<sub>21</sub>, straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> monofluoroalkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> polyfluoroalkyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkynyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, -(CH<sub>2</sub>)<sub>m</sub>-Z, or (CH<sub>2</sub>)<sub>n</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-CH<sub>3</sub>;

wherein R<sub>18</sub> is straight chained or branched C<sub>1</sub>-C<sub>6</sub> alkyl, -(CH<sub>2</sub>)<sub>m</sub>-Z, or (CH<sub>2</sub>)<sub>q</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-CH<sub>3</sub>;

wherein each R<sub>19</sub> is independently H, or straight chained or branched C<sub>1</sub>-C<sub>6</sub> alkyl;

wherein each R<sub>20</sub> is independently -H; straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl or alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl or C<sub>5</sub>-C<sub>7</sub> cycloalkenyl; -F, -Cl, -Br, or -I; -NO<sub>2</sub>; -N<sub>3</sub>; -CN; -OR<sub>21</sub>, -OCOR<sub>21</sub>, -COR<sub>21</sub>, -NCOR<sub>21</sub>, -N(R<sub>21</sub>)<sub>2</sub>, -CON(R<sub>21</sub>)<sub>2</sub>, or -COOR<sub>21</sub>; aryl or heteroaryl; or two R<sub>20</sub> groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each R<sub>21</sub> is independently -H; straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl or alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, aryl, or aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl;

wherein each R<sub>22</sub> is independently H, F, Cl or C<sub>1</sub>-C<sub>4</sub> straight chained or branched alkyl;

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

wherein p is an integer from 0 to 2 inclusive;

5

wherein q is an integer from 2 to 4 inclusive;

wherein t is 1 or 2;

10

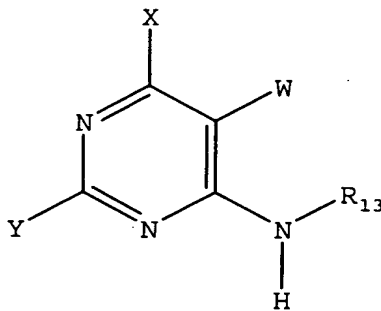
wherein U is O,  $-NR_{16}$ , S,  $C(R_{17})_2$ , or  $-NSO_2R_{16}$ ;

wherein Z is  $C_3-C_{10}$  cycloalkyl,  $C_4-C_7$  cyclic ether,  $C_4-C_7$  cyclic thioether, aryl, or heteroaryl; or

15

a pharmaceutically acceptable salt thereof.

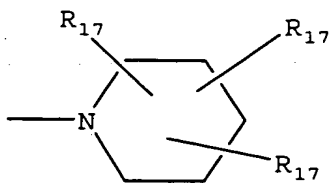
The invention provides a compound having the structure:



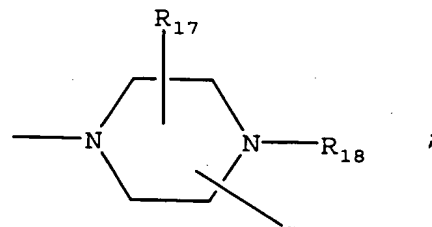
20

wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

wherein X is  $NR_{11}R_{12}$ ;



; or



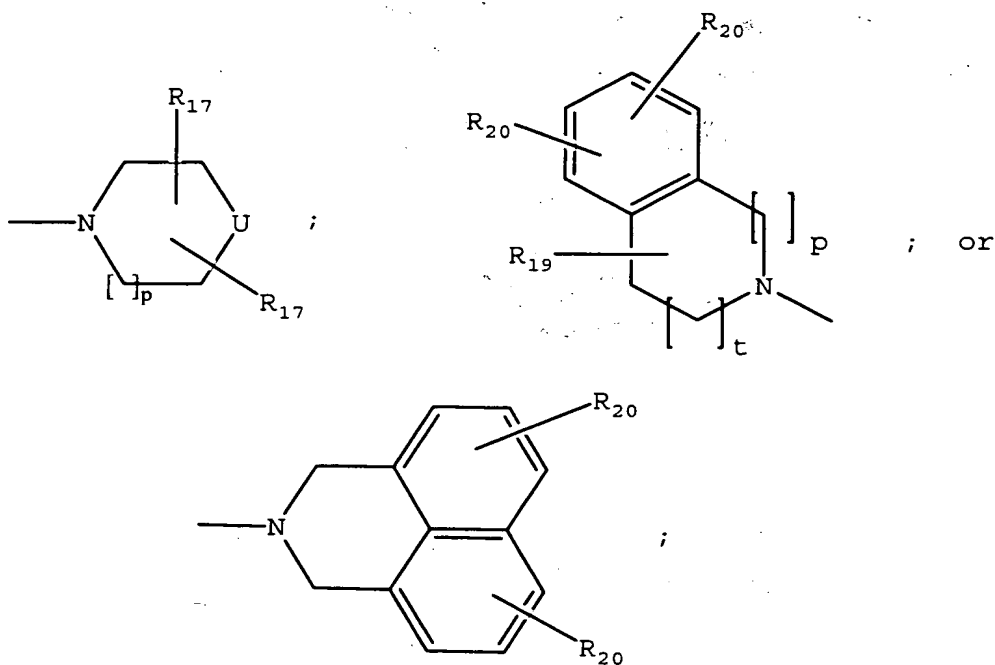
wherein  $R_{11}$  is H, straight chained or branched  $C_1$ - $C_7$  alkyl,  $(CH_2)_q$ -O- $(CH_2)_m$ - $CH_3$ , aryl or aryl( $C_1$ - $C_6$ )alkyl;

5 wherein  $R_{12}$  is straight chained or branched  $C_1$ - $C_7$  alkyl,  $(CH_2)_q$ -O- $(CH_2)_m$ - $CH_3$ , or  $-(CH_2)_m$ -Z;

wherein  $R_{13}$  is a bicyclic alkyl ring system, aryl or aryl( $C_1$ - $C_6$ )alkyl;

10

wherein Y is  $NR_{14}R_{15}$ ;



15

wherein  $R_{14}$  is H, straight chained or branched  $C_1$ - $C_6$  alkyl,  $(CH_2)_q$ -O- $(CH_2)_m$ - $CH_3$ ,  $C_3$ - $C_6$  cycloalkyl, or  $(C(R_{19})_2)_m$ -Z;

wherein  $R_{15}$  is straight chained or branched  $C_3$ - $C_6$  alkyl,

$(\text{CH}_2)_q\text{-O-}(\text{CH}_2)_m\text{-CH}_3$ ,  $\text{C}_3\text{-C}_6$  cycloalkyl, or  $(\text{C}(\text{R}_{19})_2)_m\text{-Z}$ ;

wherein U is O,  $-\text{NR}_{16}$ , S,  $\text{C}(\text{R}_{17})_2$ , or  $-\text{NSO}_2\text{R}_{16}$ ;

5 wherein Z is  $\text{C}_3\text{-C}_{10}$  cycloalkyl, aryl, or heteroaryl;

wherein  $\text{R}_{16}$  is straight chained or branched  $\text{C}_1\text{-C}_7$  alkyl,  
 straight chained or branched  $\text{C}_1\text{-C}_7$  monofluoroalkyl,  
 straight chained or branched  $\text{C}_1\text{-C}_7$  polyfluoroalkyl,  
 10 straight chained or branched  $\text{C}_2\text{-C}_7$  alkenyl, straight  
 chained or branched  $\text{C}_2\text{-C}_7$  alkynyl,  $\text{C}_5\text{-C}_7$  cycloalkenyl, -  
 $(\text{CH}_2)_m\text{-Z}$ , or  $(\text{CH}_2)_q\text{-O-}(\text{CH}_2)_m\text{-CH}_3$ ;

wherein each  $\text{R}_{17}$  is independently H;  $-\text{OR}_{21}$ ,  $-\text{OCOR}_{21}$ ,  $-\text{COR}_{21}$ ,  
 15  $-\text{NCOR}_{21}$ ,  $-\text{N}(\text{R}_{21})_2$ ,  $-\text{CON}(\text{R}_{21})_2$ ,  $-\text{COOR}_{21}$ , straight chained or  
 branched  $\text{C}_1\text{-C}_7$  alkyl, straight chained or branched  $\text{C}_1\text{-C}_7$   
 monofluoroalkyl, straight chained or branched  $\text{C}_1\text{-C}_7$   
 polyfluoroalkyl, straight chained or branched  $\text{C}_2\text{-C}_7$   
 alkenyl, straight chained or branched  $\text{C}_2\text{-C}_7$  alkynyl,  $\text{C}_5\text{-C}_7$   
 20 cycloalkenyl,  $-(\text{CH}_2)_m\text{-Z}$ , or  $(\text{CH}_2)_n\text{-O-}(\text{CH}_2)_m\text{-CH}_3$ ;

wherein  $\text{R}_{18}$  is straight chained or branched  $\text{C}_1\text{-C}_6$  alkyl, -  
 $(\text{CH}_2)_m\text{-Z}$ , or  $(\text{CH}_2)_q\text{-O-}(\text{CH}_2)_m\text{-CH}_3$ ;

25 wherein each  $\text{R}_{19}$  is independently H, or straight chained  
 or branched  $\text{C}_1\text{-C}_6$  alkyl;

wherein each  $\text{R}_{20}$  is independently -H; straight chained or  
 branched  $\text{C}_1\text{-C}_7$  alkyl, monofluoroalkyl or polyfluoroalkyl;  
 30 straight chained or branched  $\text{C}_2\text{-C}_7$  alkenyl or alkynyl;  $\text{C}_3\text{-C}_7$   
 cycloalkyl or  $\text{C}_5\text{-C}_7$  cycloalkenyl; -F, -Cl, -Br, or -I;  
 $-\text{NO}_2$ ;  $-\text{N}_3$ ;  $-\text{CN}$ ;  $-\text{OR}_{21}$ ,  $-\text{OCOR}_{21}$ ,  $-\text{COR}_{21}$ ,  $-\text{NCOR}_{21}$ ,  $-\text{N}(\text{R}_{21})_2$ , -



CON(R<sub>21</sub>)<sub>2</sub>, or -COOR<sub>21</sub>; aryl or heteroaryl; or two R<sub>20</sub> groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

5        wherein each R<sub>21</sub> is independently -H; straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl or alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, aryl or aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl;

10

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

15

wherein p is an integer from 0 to 2 inclusive;

wherein q is an integer from 2 to 4 inclusive;

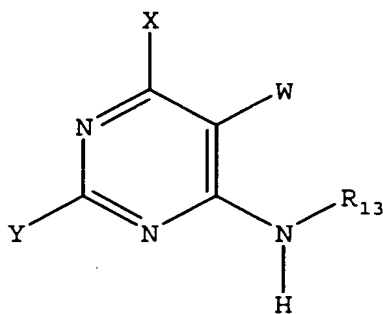
20

wherein t is 1 or 2; or

a pharmaceutically acceptable salt thereof.

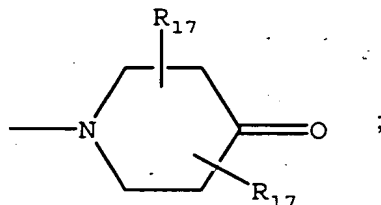
25

The invention provides a compound having the structure:



wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

5 wherein X is  $N(CH_3)_2$  or

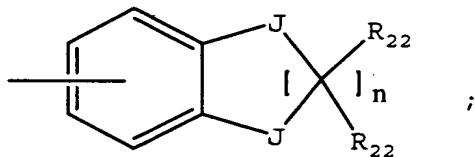


10 wherein  $R_{13}$  is an aryl, adamantyl, noradamantyl,  $C_3$ - $C_{10}$  cycloalkyl, heteroaryl,  $Q_1$  or  $Q_2$ ;

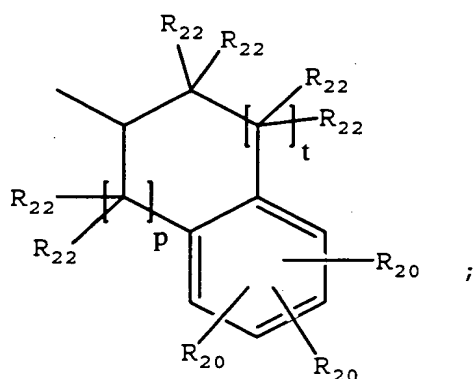
wherein aryl may be substituted with one or more  $C_1$ - $C_{10}$  straight chained or branched alkyl, aryl, heteroaryl, or  $N(R_{19})-Z$ ;

15

wherein  $Q_1$  is



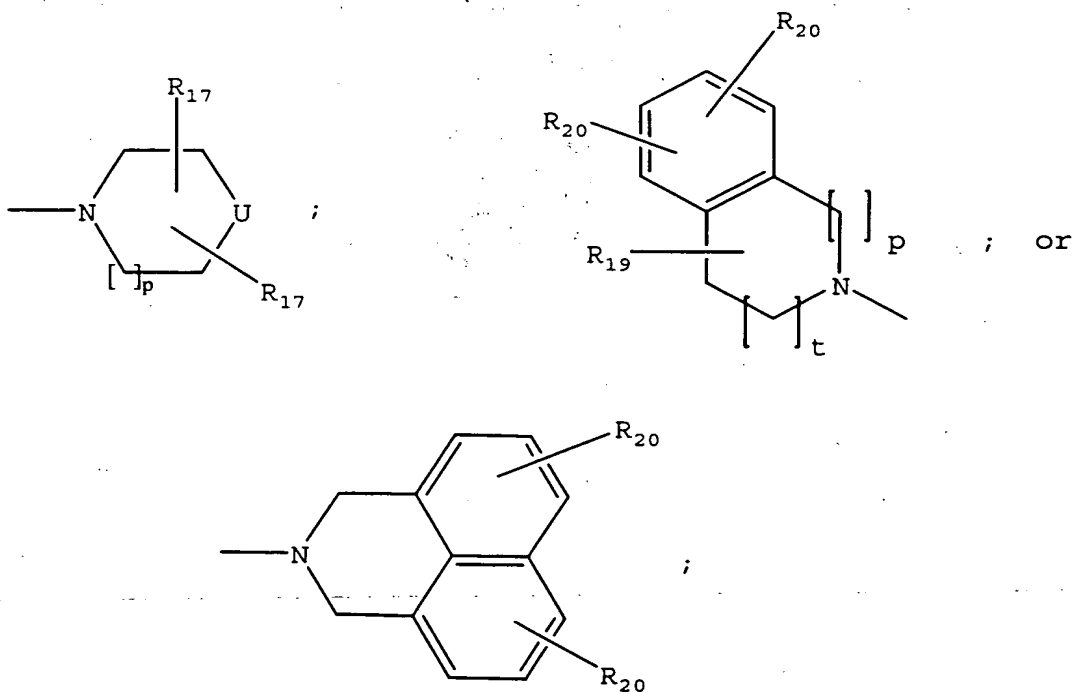
wherein  $Q_2$  is



5 wherein each J is independently O, S,  $C(R_{22})_2$  or  $NR_4$ ;

wherein  $R_4$  is -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight  
 10 chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$  cycloalkenyl or aryl;

wherein Y is  $NR_{14}R_{15}$ ;



wherein  $R_{14}$  is H, straight chained or branched  $C_1-C_6$  alkyl,  $(CH_2)_q-O-(CH_2)_m-CH_3$ ,  $C_3-C_6$  cycloalkyl, or  $(C(R_{19})_2)_m-Z$ ;

5

wherein  $R_{15}$  is straight chained or branched  $C_3-C_6$  alkyl,  $(CH_2)_q-O-(CH_2)_m-CH_3$ ,  $C_3-C_6$  cycloalkyl, or  $(C(R_{19})_2)_m-Z$ ;

wherein U is O,  $-NR_{16}$ , S,  $C(R_{17})_2$ , or  $-NSO_2R_{16}$ ;

10

wherein Z is  $C_3-C_{10}$  cycloalkyl, aryl, or heteroaryl;

wherein  $R_{16}$  is straight chained or branched  $C_1-C_7$  alkyl, straight chained or branched  $C_1-C_7$  monofluoroalkyl, straight chained or branched  $C_1-C_7$  polyfluoroalkyl, straight chained or branched  $C_2-C_7$  alkenyl, straight chained or branched  $C_2-C_7$  alkynyl,  $C_5-C_7$  cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_q-O-(CH_2)_m-CH_3$ ;

15

wherein each  $R_{17}$  is independently H,  $-OR_{21}$ ,  $-OCOR_{21}$ ,  $-COR_{21}$ ,  $-NCOR_{21}$ ,  $-N(R_{21})_2$ ,  $-CON(R_{21})_2$ ,  $-COOR_{21}$ , straight chained or branched  $C_1-C_7$  alkyl, straight chained or branched  $C_1-C_7$  monofluoroalkyl, straight chained or branched  $C_1-C_7$  polyfluoroalkyl, straight chained or branched  $C_2-C_7$  alkenyl, straight chained or branched  $C_2-C_7$  alkynyl,  $C_5-C_7$  cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_n-O-(CH_2)_m-CH_3$ ;

20

25

wherein  $R_{18}$  is straight chained or branched  $C_1-C_6$  alkyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_q-O-(CH_2)_m-CH_3$ ;

30

wherein each  $R_{19}$  is independently H, or straight chained or branched  $C_1-C_6$  alkyl;

wherein each  $R_{20}$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ -  
 5  $C_7$  cycloalkyl or  $C_5$ - $C_7$  cycloalkenyl; -F, -Cl, -Br, or -I; - $NO_2$ ; - $N_3$ ; -CN; - $OR_{21}$ , - $OCOR_{21}$ , - $COR_{21}$ , - $NCOR_{21}$ , - $N(R_{21})_2$ , - $CON(R_{21})_2$ , or - $COOR_{21}$ ; aryl or heteroaryl; or two  $R_{20}$  groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

10

wherein each  $R_{21}$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ -  
 15  $C_7$  cycloalkyl,  $C_5$ - $C_7$  cycloalkenyl, aryl or aryl( $C_1$ - $C_6$ )alkyl;

wherein each  $R_{22}$  is independently H, F, Cl or  $C_1$ - $C_4$  straight chained or branched alkyl;

20 wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

wherein p is an integer from 0 to 2 inclusive;

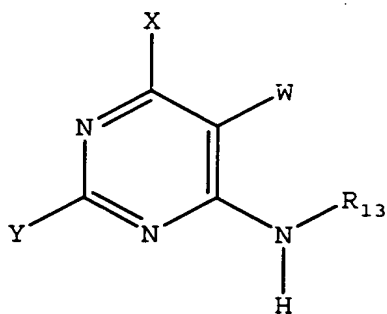
25

wherein q is an integer from 2 to 4 inclusive;

wherein t is 1 or 2; or

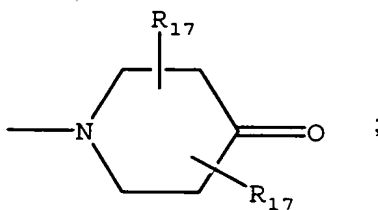
30 a pharmaceutically acceptable salt thereof.

The invention provides a compound having the structure:



wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl,  
 5 propyl, methoxy or ethoxy;

wherein X is  $N(CH_3)_2$  or



10

wherein  $R_{13}$  is a bicyclic alkyl ring system, aryl or  
 aryl( $C_1$ - $C_6$ )alkyl;

wherein Y is  $NR_{14}R_{15}$ ;

15

wherein  $R_{14}$  is H, straight chained or branched  $C_1$ - $C_6$  alkyl,  
 $(CH_2)_q-O-(CH_2)_m-CH_3$ ,  $C_3$ - $C_6$  cycloalkyl, or  $(C(R_{19})_2)_m-Z$ ;

wherein  $R_{15}$  is  $(C(R_{19})_2)_m-N(R_{16})_2$ ;

20

wherein Z is  $C_3$ - $C_{10}$  cycloalkyl, aryl, or heteroaryl;

wherein  $R_{16}$  is straight chained or branched  $C_1$ - $C_7$  alkyl, straight chained or branched  $C_1$ - $C_7$  monofluoroalkyl, straight chained or branched  $C_1$ - $C_7$  polyfluoroalkyl, straight chained or branched  $C_2$ - $C_7$  alkenyl, straight  
 5 chained or branched  $C_2$ - $C_7$  alkynyl,  $C_5$ - $C_7$  cycloalkenyl, -  
 $(CH_2)_m$ -Z, or  $(CH_2)_q$ -O- $(CH_2)_m$ -CH<sub>3</sub>;

wherein each  $R_{17}$  is independently H; -OR<sub>21</sub>, -OCOR<sub>21</sub>, -COR<sub>21</sub>,  
 -NCOR<sub>21</sub>, -N(R<sub>21</sub>)<sub>2</sub>, -CON(R<sub>21</sub>)<sub>2</sub>, -COOR<sub>21</sub>, straight chained or  
 10 branched  $C_1$ - $C_7$  alkyl, straight chained or branched  $C_1$ - $C_7$   
 monofluoroalkyl, straight chained or branched  $C_1$ - $C_7$   
 polyfluoroalkyl, straight chained or branched  $C_2$ - $C_7$   
 alkenyl, straight chained or branched  $C_2$ - $C_7$  alkynyl,  $C_5$ - $C_7$   
 cycloalkenyl, - $(CH_2)_m$ -Z, or  $(CH_2)_n$ -O- $(CH_2)_m$ -CH<sub>3</sub>;

15 wherein each  $R_{19}$  is independently H, or straight chained  
 or branched  $C_1$ - $C_6$  alkyl;

wherein each  $R_{21}$  is independently -H; straight chained or  
 20 branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl;  
 straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ -  
 $C_7$  cycloalkyl,  $C_5$ - $C_7$  cycloalkenyl, aryl or aryl( $C_1$ -  
 $C_6$ )alkyl;

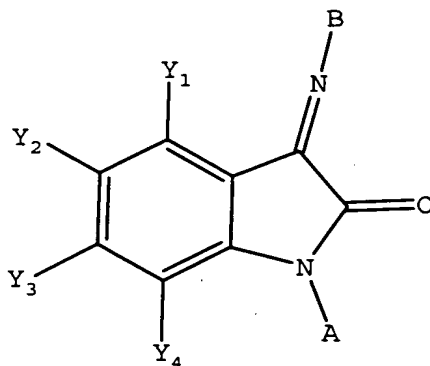
25 wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

wherein q is an integer from 2 to 4 inclusive; or

30 a pharmaceutically acceptable salt thereof.

The invention also provides a method of treating a subject suffering from depression which comprises administering to the subject an amount of compound effective to treat the subject's depression wherein the compound has the structure:



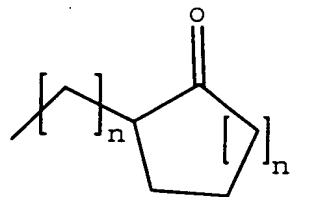
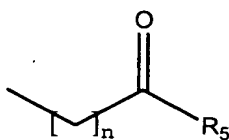
wherein each of  $Y_1$ ,  $Y_2$ ,  $Y_3$ , and  $Y_4$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl, or  $C_5$ - $C_7$  cycloalkenyl; -F, -Cl, -Br, or -I; - $NO_2$ ; - $N_3$ ; -CN; - $OR_4$ , - $SR_4$ , - $OCOR_4$ , - $COR_4$ , - $NCOR_4$ , - $N(R_4)_2$ , - $CON(R_4)_2$ , or - $COOR_4$ ; aryl or heteroaryl; or any two of  $Y_1$ ,  $Y_2$ ,  $Y_3$  and  $Y_4$  present on adjacent carbon atoms can constitute a methylenedioxy group;

wherein each  $R_4$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$  cycloalkenyl, aryl or aryl( $C_1$ - $C_6$ )alkyl;

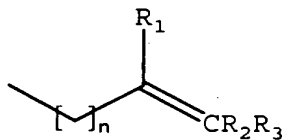


5 wherein A is A', Q<sub>3</sub>, Q<sub>4</sub>, Q<sub>5</sub>, straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, aryl, heteroaryl, aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl, heteroaryl(C<sub>1</sub>-C<sub>6</sub>)alkyl, aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl; or (CHR<sub>17</sub>)-(CHR<sub>17</sub>)<sub>n</sub>-Z;

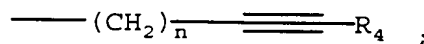
wherein A' is



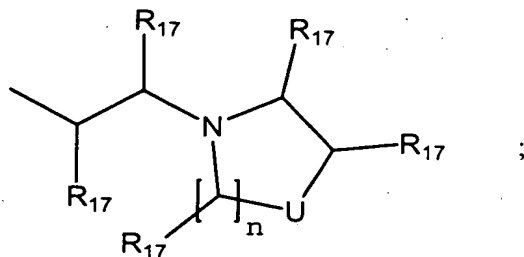
10



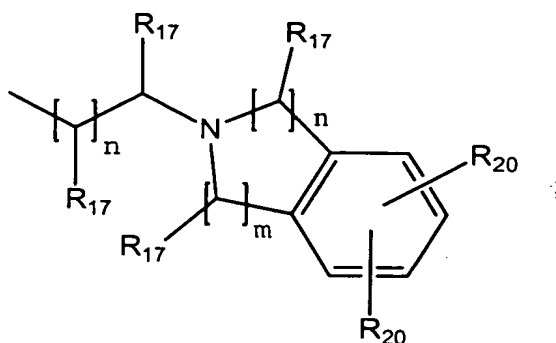
; or



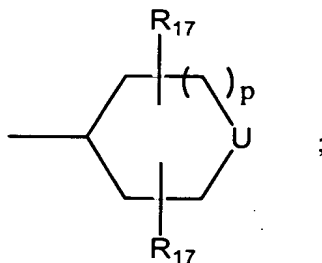
15 wherein Q<sub>3</sub> is



5 wherein Q<sub>4</sub> is



wherein Q<sub>5</sub> is



10

wherein R<sub>1</sub> and R<sub>2</sub> are each independently H, straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, -F, -Cl, -Br, -I, -NO<sub>2</sub>, or -CN;

15 wherein R<sub>3</sub> is H, straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, -F, -Cl, -Br, -I, -NO<sub>2</sub>, -CN, -OR<sub>6</sub>, aryl or heteroaryl;

20 wherein R<sub>5</sub> is straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, -N(R<sub>4</sub>)<sub>2</sub>, -OR<sub>6</sub> or aryl;

wherein  $R_6$  is straight chained or branched  $C_1$ - $C_7$  alkyl or aryl;

5            wherein each  $R_{17}$  is independently H; straight chained or branched  $C_1$ - $C_7$  alkyl, straight chained or branched  $C_1$ - $C_7$  monofluoroalkyl, straight chained or branched  $C_1$ - $C_7$  polyfluoroalkyl, straight chained or branched  $C_2$ - $C_7$  alkenyl, straight chained or branched  $C_2$ - $C_7$  alkynyl,  $C_5$ - $C_7$  cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_n-O-(CH_2)_m-CH_3$ ;  
10

           wherein each  $R_{20}$  is independently -H; straight  
           chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or  
15            polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl or  $C_5$ - $C_7$  cycloalkenyl; -F, -Cl, -Br, or -I; -NO<sub>2</sub>; -N<sub>3</sub>; -CN; -OR<sub>21</sub>, -OCOR<sub>21</sub>, -COR<sub>21</sub>, -NCOR<sub>21</sub>, -N(R<sub>21</sub>)<sub>2</sub>, -CON(R<sub>21</sub>)<sub>2</sub>, or -COOR<sub>21</sub>; aryl or heteroaryl; or two  $R_{20}$  groups present  
20            on adjacent carbon atoms can join together to form a methylenedioxy group;

           wherein each  $R_{21}$  is independently -H; straight  
           chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or  
25            polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$  cycloalkenyl, aryl or aryl( $C_1$ - $C_6$ )alkyl;

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

5 wherein each p is an integer from 0 to 2 inclusive;

wherein U is O,  $-NR_{16}$ , S,  $C(R_{17})_2$ , or  $-NSO_2R_{16}$ ;

10 wherein Z is  $C_3-C_{10}$  cycloalkyl,  $C_4-C_7$  cyclic ether,  $C_4-C_7$  cyclic thioether, aryl, or heteroaryl;

15 wherein  $R_{16}$  is straight chained or branched  $C_1-C_7$  alkyl, straight chained or branched  $C_1-C_7$  monofluoroalkyl, straight chained or branched  $C_1-C_7$  polyfluoroalkyl, straight chained or branched  $C_2-C_7$  alkenyl, straight chained or branched  $C_2-C_7$  alkynyl,  $C_5-C_7$  cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_q-O-(CH_2)_m-CH_3$ ;

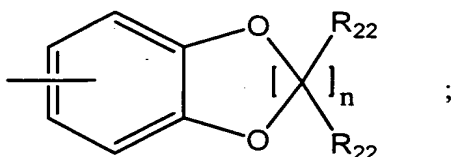
20 wherein q is an integer from 2 to 4 inclusive;

25 wherein B is aryl, heteroaryl, aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl, tricyclic heteroaryl or  $Q_6$ ; provided however, if B is aryl or heteroaryl the carbon atom or carbon atoms ortho to the nitrogen atom of the imine bond may only be substituted with one or more of the following -F, -Cl, -Br, -I, -CN, methyl, ethyl or methoxy;

wherein a tricyclic heteroaryl is a fused three member aromatic system in which one or more of the rings is heteroaryl; carbazole; or acridine;

5

wherein  $Q_6$  is



10

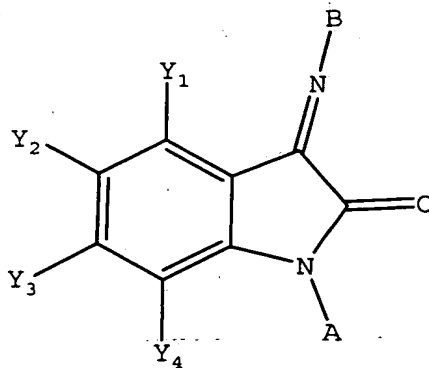
wherein each  $R_{22}$  is independently H, F, Cl, or straight chained or branched  $C_1$ - $C_4$  alkyl;

or a pharmaceutically acceptable salt thereof.

15

The invention provides a method of treating a subject suffering from depression which comprises administering to the subject an amount of compound effective to treat the subject's depression wherein the compound has the structure:

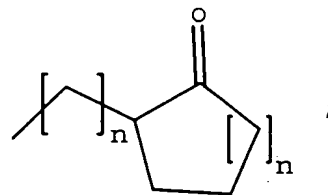
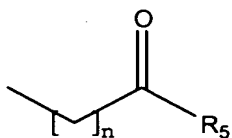
20



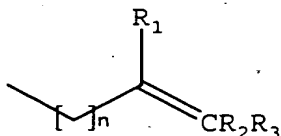
wherein each of  $Y_1$ ,  $Y_2$ ,  $Y_3$ , and  $Y_4$  is independently -  
 H; straight chained or branched  $C_1$ - $C_7$  alkyl,  
 monofluoroalkyl or polyfluoroalkyl; straight chained  
 5 or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$   
 cycloalkyl, or  $C_5$ - $C_7$  cycloalkenyl; -F, -Cl, -Br, or -  
 I; - $NO_2$ ; - $N_3$ ; -CN; - $OR_4$ , - $SR_4$ , - $OCOR_4$ , - $COR_4$ , - $NCOR_4$ , -  
 $N(R_4)_2$ , - $CON(R_4)_2$ , or - $COOR_4$ ; aryl or heteroaryl; or  
 10 any two of  $Y_1$ ,  $Y_2$ ,  $Y_3$  and  $Y_4$  present on adjacent  
 carbon atoms can constitute a methylenedioxy group;

wherein each  $R_4$  is independently -H; straight chained  
 or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or  
 polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$   
 15 alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$   
 cycloalkenyl, aryl or aryl( $C_1$ - $C_6$ )alkyl;

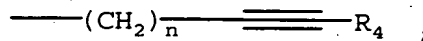
wherein A is A', straight chained or branched  $C_1$ - $C_7$   
 alkyl, aryl, heteroaryl, aryl( $C_1$ - $C_6$ )alkyl or  
 20 heteroaryl( $C_1$ - $C_6$ )alkyl;



wherein A' is



; or



5            wherein  $R_1$  and  $R_2$  are each independently H, straight  
             chained or branched  $C_1$ - $C_7$  alkyl, -F, -Cl, -Br, -I, -  
              $NO_2$ , or -CN;

             wherein  $R_3$  is H, straight chained or branched  $C_1$ - $C_7$   
10            alkyl, -F, -Cl, -Br, -I, - $NO_2$ , -CN, -OR<sub>6</sub> aryl or  
             heteroaryl;

             wherein  $R_5$  is straight chained or branched  $C_1$ - $C_7$   
             alkyl, -N( $R_4$ )<sub>2</sub>, -OR<sub>6</sub> or aryl;

15            wherein  $R_6$  is straight chained or branched  $C_1$ - $C_7$   
             alkyl or aryl;

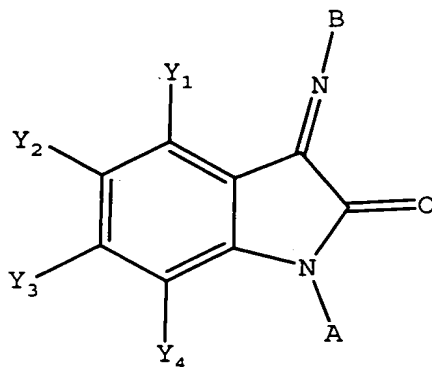
             wherein B is aryl, or heteroaryl; provided however,  
20            if B is aryl or heteroaryl the carbon atom or carbon  
             atoms ortho to the nitrogen atom of the imine bond  
             may only be substituted with one or more of the  
             following -F, -Cl, -Br, -I, -CN, methyl, ethyl or  
             methoxy;

25            wherein n is an integer from 1 to 4 inclusive;

             or a pharmaceutically acceptable salt thereof.

30            The invention provides a method of treating a subject  
             suffering from depression which comprises administering  
             to the subject an amount of compound effective to treat

the subject's depression wherein the compound has the structure:



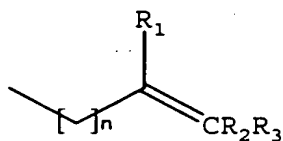
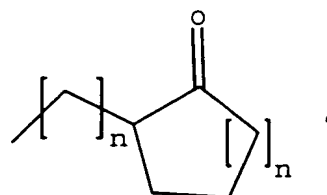
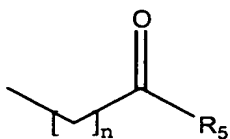
5            wherein each of  $Y_1$ ,  $Y_2$ ,  $Y_3$ , and  $Y_4$  is independently -  
              H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained  
              or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$   
              cycloalkyl, or  $C_5$ - $C_7$  cycloalkenyl; -F, -Cl, -Br, or -  
 10            I; - $NO_2$ ; - $N_3$ ; -CN; - $OR_4$ , - $SR_4$ , - $OCOR_4$ , - $COR_4$ , - $NCOR_4$ , -  
               $N(R_4)_2$ , - $CON(R_4)_2$ , or - $COOR_4$ ; aryl or heteroaryl; or  
              any two of  $Y_1$ ,  $Y_2$ ,  $Y_3$  and  $Y_4$  present on adjacent  
              carbon atoms can constitute a methylenedioxy group;

15            wherein each  $R_4$  is independently -H; straight chained  
              or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or  
              polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$   
              alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$   
              cycloalkenyl, aryl or aryl( $C_1$ - $C_6$ )alkyl;

20            wherein A is A', straight chained or branched  $C_1$ - $C_7$   
              alkyl, aryl, heteroaryl, aryl( $C_1$ - $C_6$ )alkyl or  
              heteroaryl( $C_1$ - $C_6$ )alkyl;



wherein A' is



; or



5

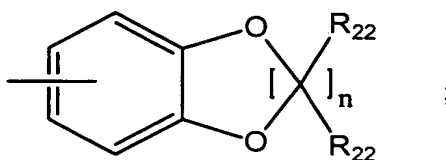
wherein B is aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl, tricyclic heteroaryl or Q<sub>6</sub>;

10

wherein a tricyclic heteroaryl is a fused three ring aromatic system in which one or more of the rings is heteroaryl; carbazole; or acridine;

15

wherein Q<sub>6</sub> is



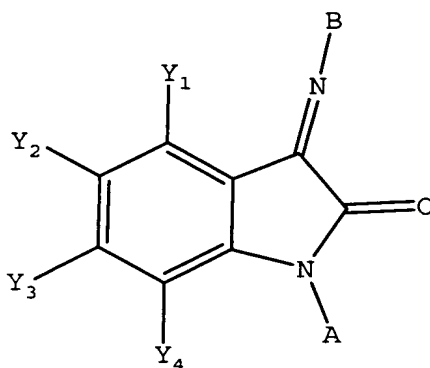
20

wherein n is an integer from 1 to 4 inclusive;

wherein each  $R_{22}$  is independently H, F, Cl, or straight chained or branched  $C_1$ - $C_4$  alkyl;

5 or a pharmaceutically acceptable salt thereof.

The invention provides a method of treating a subject  
 10 suffering from depression which comprises administering  
 to the subject an amount of compound effective to treat  
 the subject's depression wherein the compound has the  
 structure:



15

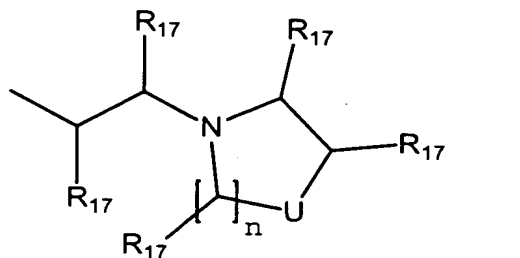
wherein each of  $Y_1$ ,  $Y_2$ ,  $Y_3$ , and  $Y_4$  is independently -  
 H; straight chained or branched  $C_1$ - $C_7$  alkyl,  
 monofluoroalkyl or polyfluoroalkyl; straight chained  
 or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$   
 20 cycloalkyl, or  $C_5$ - $C_7$  cycloalkenyl; -F, -Cl, -Br, or -  
 I; - $NO_2$ ; - $N_3$ ; -CN; - $OR_4$ , - $SR_4$ , - $OCOR_4$ , - $COR_4$ , - $NCOR_4$ , -  
 $N(R_4)_2$ , - $CON(R_4)_2$ , or - $COOR_4$ ; aryl or heteroaryl; or  
 any two of  $Y_1$ ,  $Y_2$ ,  $Y_3$  and  $Y_4$  present on adjacent  
 carbon atoms can constitute a methylenedioxy group;

25

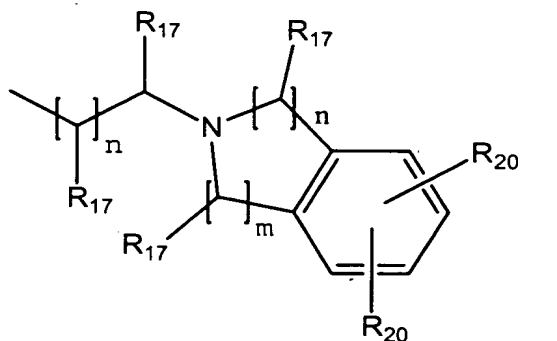
wherein each  $R_4$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$  cycloalkenyl, aryl or aryl( $C_1$ - $C_6$ )alkyl;

wherein A is  $Q_3$ ,  $Q_4$ ,  $Q_5$ , aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl, or  $(CHR_{17}) - (CHR_{17})_n - Z$ ;

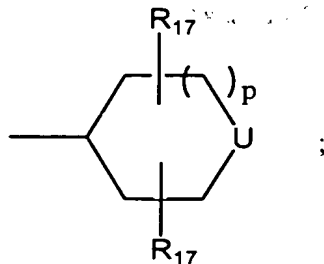
wherein  $Q_3$  is



wherein  $Q_4$  is



wherein  $Q_5$  is



5 wherein each  $R_{17}$  is independently H; straight chained  
or branched  $C_1$ - $C_7$  alkyl, straight chained or branched  
 $C_1$ - $C_7$  monofluoroalkyl, straight chained or branched  
 $C_1$ - $C_7$  polyfluoroalkyl, straight chained or branched  
 $C_2$ - $C_7$  alkenyl, straight chained or branched  $C_2$ - $C_7$   
alkynyl,  $C_5$ - $C_7$  cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_n-O-$   
10  $(CH_2)_m-CH_3$ ;

wherein each  $R_{20}$  is independently -H; straight  
chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or  
polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$   
15 alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl or  $C_5$ - $C_7$   
cycloalkenyl; -F, -Cl, -Br, or -I; -NO<sub>2</sub>; -N<sub>3</sub>; -CN; -  
OR<sub>21</sub>, -OCOR<sub>21</sub>, -COR<sub>21</sub>, -NCOR<sub>21</sub>, -N(R<sub>21</sub>)<sub>2</sub>, -CON(R<sub>21</sub>)<sub>2</sub>, or  
-COOR<sub>21</sub>; aryl or heteroaryl; or two  $R_{20}$  groups present  
on adjacent carbon atoms can join together to form a  
20 methylenedioxy group;

wherein each  $R_{21}$  is independently -H; straight  
chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or  
polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$   
25 alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$   
cycloalkenyl or aryl;

wherein each  $R_{22}$  is independently H, F, Cl, or straight chained or branched  $C_1$ - $C_4$  alkyl;

wherein each m is an integer from 0 to 4 inclusive;

5

wherein each n is an integer from 1 to 4 inclusive;

wherein each p is an integer from 0 to 2 inclusive;

10

wherein U is O,  $-NR_{16}$ , S,  $C(R_{17})_2$ , or  $-NSO_2R_{16}$ ;

wherein Z is  $C_3$ - $C_{10}$  cycloalkyl,  $C_4$ - $C_7$  cyclic ether,  $C_4$ - $C_7$  cyclic thioether, aryl, or heteroaryl;

15

wherein  $R_{16}$  is straight chained or branched  $C_1$ - $C_7$  alkyl, straight chained or branched  $C_1$ - $C_7$  monofluoroalkyl, straight chained or branched  $C_1$ - $C_7$  polyfluoroalkyl, straight chained or branched  $C_2$ - $C_7$  alkenyl, straight chained or branched  $C_2$ - $C_7$  alkynyl,  $C_5$ - $C_7$  cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_q-O-(CH_2)_m-CH_3$ ;

20

wherein q is an integer from 2 to 4 inclusive;

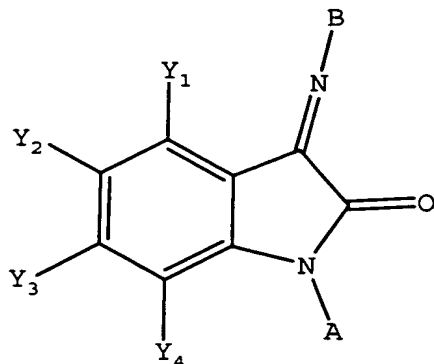
25

wherein B is aryl, or heteroaryl; provided however, if B is aryl or heteroaryl the carbon atom or carbon atoms ortho to the nitrogen atom of the imine bond may only be substituted with one or more of the following -F, -Cl, -Br, -I, -CN, methyl, ethyl or methoxy;

30

or a pharmaceutically acceptable salt thereof.

The invention provides a method of treating a subject suffering from anxiety which comprises administering to the subject an amount of compound effective to treat the subject's anxiety wherein the compound has the structure:



wherein each of  $Y_1$ ,  $Y_2$ ,  $Y_3$ , and  $Y_4$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl, or  $C_5$ - $C_7$  cycloalkenyl; -F, -Cl, -Br, or -I; - $NO_2$ ; - $N_3$ ; -CN; - $OR_4$ , - $SR_4$ , - $OCOR_4$ , - $COR_4$ , - $NCOR_4$ , - $N(R_4)_2$ , - $CON(R_4)_2$ , or - $COOR_4$ ; aryl or heteroaryl; or any two of  $Y_1$ ,  $Y_2$ ,  $Y_3$  and  $Y_4$  present on adjacent carbon atoms can constitute a methylenedioxy group;

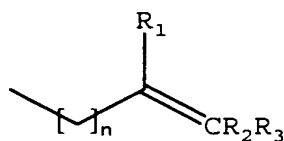
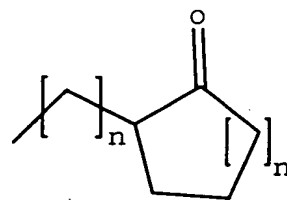
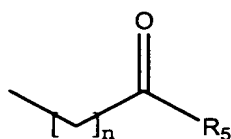
wherein each  $R_4$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$  cycloalkenyl, aryl or aryl( $C_1$ - $C_6$ )alkyl;

wherein A is  $A'$ ,  $Q_3$ ,  $Q_4$ ,  $Q_5$ , straight chained or

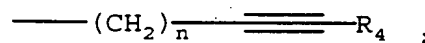
branched  $C_1$ - $C_7$  alkyl, aryl, heteroaryl, aryl( $C_1$ - $C_6$ )alkyl, heteroaryl( $C_1$ - $C_6$ )alkyl, aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl; or  $(CHR_{17})_n - (CHR_{17})_n - Z$ ;

5

wherein  $A'$  is

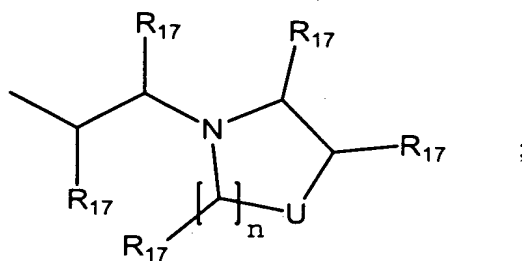


; or



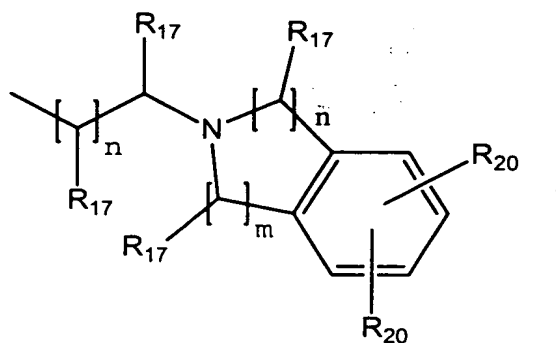
10

wherein  $Q_3$  is



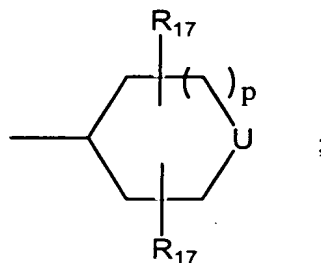
15

wherein  $Q_4$  is



5

wherein  $Q_5$  is



10

wherein  $R_1$  and  $R_2$  are each independently H, straight chained or branched  $C_1$ - $C_7$  alkyl, -F, -Cl, -Br, -I, - $NO_2$ , or -CN;

15

wherein  $R_3$  is H, straight chained or branched  $C_1$ - $C_7$  alkyl, -F, -Cl, -Br, -I, - $NO_2$ , -CN, - $OR_6$ , aryl or heteroaryl;

wherein  $R_5$  is straight chained or branched  $C_1$ - $C_7$  alkyl, - $N(R_4)_2$ , - $OR_6$  or aryl;



wherein  $R_6$  is straight chained or branched  $C_1$ - $C_7$  alkyl or aryl;

5 wherein each  $R_{17}$  is independently H; straight chained or branched  $C_1$ - $C_7$  alkyl, straight chained or branched  $C_1$ - $C_7$  monofluoroalkyl, straight chained or branched  $C_1$ - $C_7$  polyfluoroalkyl, straight chained or branched  $C_2$ - $C_7$  alkenyl, straight chained or branched  $C_2$ - $C_7$  alkynyl,  $C_5$ - $C_7$  cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_n-O-$   
 10  $(CH_2)_m-CH_3$ ;

wherein each  $R_{20}$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl or  $C_5$ - $C_7$  cycloalkenyl; -F, -Cl, -Br, or -I; - $NO_2$ ; - $N_3$ ; -CN; -  
 15  $OR_{21}$ , - $OCOR_{21}$ , - $COR_{21}$ , - $NCOR_{21}$ , - $N(R_{21})_2$ , - $CON(R_{21})_2$ , or - $COOR_{21}$ ; aryl or heteroaryl; or two  $R_{20}$  groups present on adjacent carbon atoms can join together to form a  
 20 methylenedioxy group;

wherein each  $R_{21}$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$  cycloalkenyl, aryl or aryl( $C_1$ - $C_6$ )alkyl;  
 25

wherein each  $m$  is an integer from 0 to 4 inclusive;

wherein each  $n$  is an integer from 1 to 4 inclusive;

wherein each  $p$  is an integer from 0 to 2 inclusive;

5 wherein  $U$  is  $O$ ,  $-NR_{16}$ ,  $S$ ,  $C(R_{17})_2$ , or  $-NSO_2R_{16}$ ;

wherein  $Z$  is  $C_3$ - $C_{10}$  cycloalkyl,  $C_4$ - $C_7$  cyclic ether,  $C_4$ - $C_7$  cyclic thioether, aryl, or heteroaryl;

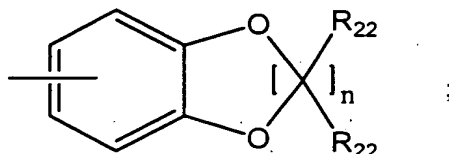
10 wherein  $R_{16}$  is straight chained or branched  $C_1$ - $C_7$  alkyl, straight chained or branched  $C_1$ - $C_7$  monofluoroalkyl, straight chained or branched  $C_1$ - $C_7$  polyfluoroalkyl, straight chained or branched  $C_2$ - $C_7$  alkenyl, straight chained or branched  $C_2$ - $C_7$  alkynyl,  
15  $C_5$ - $C_7$  cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_q-O-(CH_2)_m-CH_3$ ;

wherein  $q$  is an integer from 2 to 4 inclusive;

20 wherein  $B$  is aryl, heteroaryl, aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl, tricyclic heteroaryl or  $Q_6$ ;  
provided however, if  $B$  is aryl or heteroaryl the carbon atom or carbon atoms ortho to the nitrogen atom of the imine bond may only be substituted with  
25 one or more of the following  $-F$ ,  $-Cl$ ,  $-Br$ ,  $-I$ ,  $-CN$ , methyl, ethyl or methoxy;

wherein a tricyclic heteroaryl is a fused three member aromatic system in which one or more of the rings is heteroaryl; carbazole; or acridine;

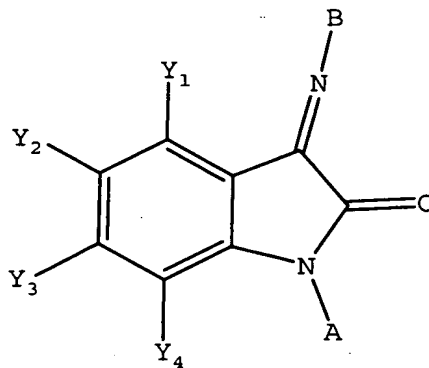
5 wherein  $Q_6$  is



10 wherein each  $R_{22}$  is independently H, F, Cl, or straight chained or branched  $C_1$ - $C_4$  alkyl;

or a pharmaceutically acceptable salt thereof.

15 The invention provides a method of treating a subject suffering from anxiety which comprises administering to the subject an amount of compound effective to treat the subject's anxiety wherein the compound has the structure:

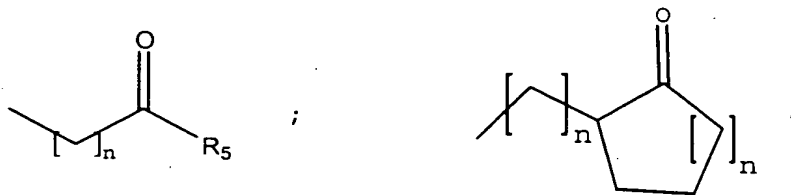


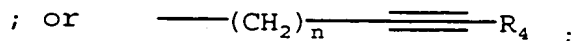
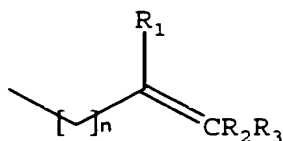
wherein each of  $Y_1$ ,  $Y_2$ ,  $Y_3$ , and  $Y_4$  is independently -  
 H; straight chained or branched  $C_1$ - $C_7$  alkyl,  
 monofluoroalkyl or polyfluoroalkyl; straight chained  
 or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$   
 cycloalkyl, or  $C_5$ - $C_7$  cycloalkenyl; -F, -Cl, -Br, or -  
 I; - $NO_2$ ; - $N_3$ ; -CN; - $OR_4$ , - $SR_4$ , - $OCOR_4$ , - $COR_4$ , - $NCOR_4$ , -  
 $N(R_4)_2$ , - $CON(R_4)_2$ , or - $COOR_4$ ; aryl or heteroaryl; or  
 any two of  $Y_1$ ,  $Y_2$ ,  $Y_3$  and  $Y_4$  present on adjacent  
 carbon atoms can constitute a methylenedioxy group;

wherein each  $R_4$  is independently -H; straight chained  
 or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or  
 polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$   
 alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$   
 cycloalkenyl, aryl or aryl( $C_1$ - $C_6$ )alkyl;

wherein A is A', straight chained or branched  $C_1$ - $C_7$   
 alkyl, aryl, heteroaryl, aryl( $C_1$ - $C_6$ )alkyl or  
 heteroaryl( $C_1$ - $C_6$ )alkyl;

wherein A' is





wherein  $R_1$  and  $R_2$  are each independently H, straight  
chained or branched  $C_1$ - $C_7$  alkyl, -F, -Cl, -Br, -I, -  
5  $\text{NO}_2$ , or -CN;

wherein  $R_3$  is H, straight chained or branched  $C_1$ - $C_7$   
alkyl, -F, -Cl, -Br, -I, - $\text{NO}_2$ , -CN, -OR<sub>6</sub> aryl or  
heteroaryl;

10 wherein  $R_5$  is straight chained or branched  $C_1$ - $C_7$   
alkyl, -N( $R_4$ )<sub>2</sub>, -OR<sub>6</sub> or aryl;

15 wherein  $R_6$  is straight chained or branched  $C_1$ - $C_7$   
alkyl or aryl;

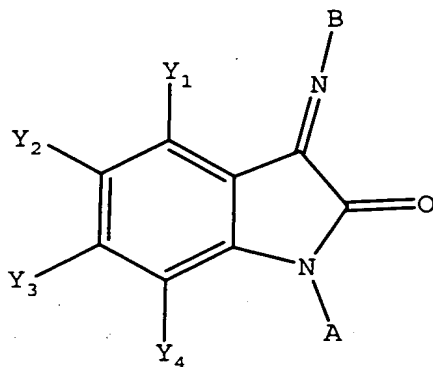
wherein B is aryl, or heteroaryl; provided however,  
if B is aryl or heteroaryl the carbon atom or carbon  
atoms ortho to the nitrogen atom of the imine bond  
20 may only be substituted with one or more of the  
following -F, -Cl, -Br, -I, -CN, methyl, ethyl or  
methoxy;

wherein n is an integer from 1 to 4 inclusive;

25 or a pharmaceutically acceptable salt thereof.

The invention provides a method of treating a subject  
suffering from anxiety which comprises administering to

the subject an amount of compound effective to treat the subject's anxiety wherein the compound has the structure:

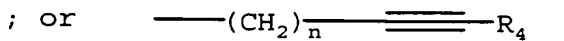
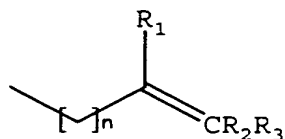
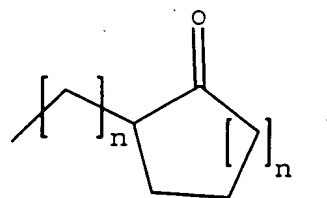
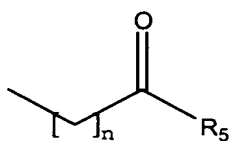


5            wherein each of  $Y_1$ ,  $Y_2$ ,  $Y_3$ , and  $Y_4$  is independently -  
H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained  
or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$   
10           cycloalkyl, or  $C_5$ - $C_7$  cycloalkenyl; -F, -Cl, -Br, or -  
I; - $NO_2$ ; - $N_3$ ; -CN; - $OR_4$ , - $SR_4$ , - $OCOR_4$ , - $COR_4$ , - $NCOR_4$ , -  
 $N(R_4)_2$ , - $CON(R_4)_2$ , or - $COOR_4$ ; aryl or heteroaryl; or  
any two of  $Y_1$ ,  $Y_2$ ,  $Y_3$  and  $Y_4$  present on adjacent  
carbon atoms can constitute a methylenedioxy group;

15           wherein each  $R_4$  is independently -H; straight chained  
or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or  
polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$   
alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$   
cycloalkenyl, aryl or aryl( $C_1$ - $C_6$ )alkyl;

20           wherein A is A', straight chained or branched  $C_1$ - $C_7$   
alkyl, aryl, heteroaryl, aryl( $C_1$ - $C_6$ )alkyl or  
heteroaryl( $C_1$ - $C_6$ )alkyl;

wherein A' is



5

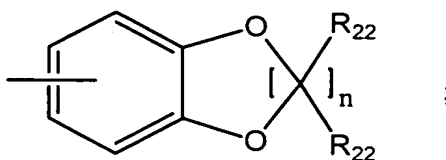
wherein B is aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl, tricyclic heteroaryl or Q<sub>6</sub>;

10

wherein a tricyclic heteroaryl is a fused three ring aromatic system in which one or more of the rings is heteroaryl; carbazole; or acridine;

15

wherein Q<sub>6</sub> is



wherein n is an integer from 1 to 4 inclusive;

20

wherein each R<sub>22</sub> is independently H, F,

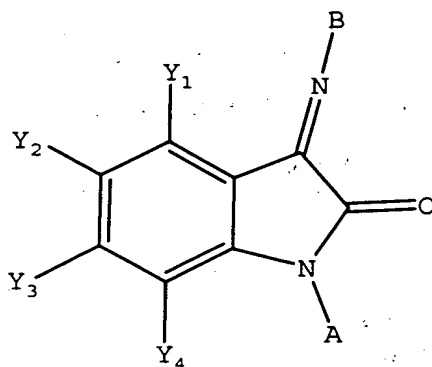
Cl, or straight chained or branched C<sub>1</sub>-C<sub>4</sub> alkyl;

or a pharmaceutically acceptable salt thereof.

5

The invention provides a method of treating a subject suffering from anxiety which comprises administering to the subject an amount of compound effective to treat the subject's anxiety wherein the compound has the structure:

10



wherein each of Y<sub>1</sub>, Y<sub>2</sub>, Y<sub>3</sub>, and Y<sub>4</sub> is independently -H; straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl or alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl, or C<sub>5</sub>-C<sub>7</sub> cycloalkenyl; -F, -Cl, -Br, or -I; -NO<sub>2</sub>; -N<sub>3</sub>; -CN; -OR<sub>4</sub>, -SR<sub>4</sub>, -OCOR<sub>4</sub>, -COR<sub>4</sub>, -NCOR<sub>4</sub>, -N(R<sub>4</sub>)<sub>2</sub>, -CON(R<sub>4</sub>)<sub>2</sub>, or -COOR<sub>4</sub>; aryl or heteroaryl; or any two of Y<sub>1</sub>, Y<sub>2</sub>, Y<sub>3</sub> and Y<sub>4</sub> present on adjacent carbon atoms can constitute a methylenedioxy group;

wherein each R<sub>4</sub> is independently -H; straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C<sub>2</sub>-C<sub>7</sub>

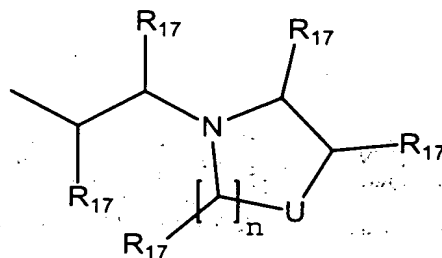
25



alkenyl or alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, aryl or aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl;

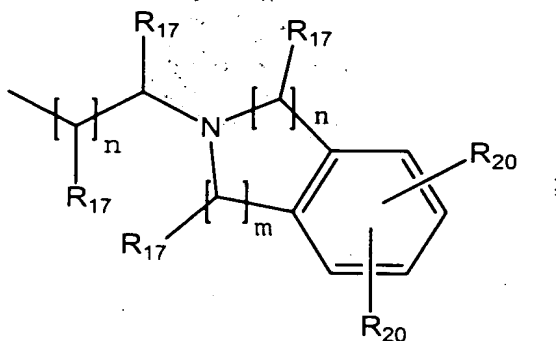
5 wherein A is Q<sub>3</sub>, Q<sub>4</sub>, Q<sub>5</sub>, aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl, or (CHR<sub>17</sub>)<sub>n</sub>-Z;

wherein Q<sub>3</sub> is

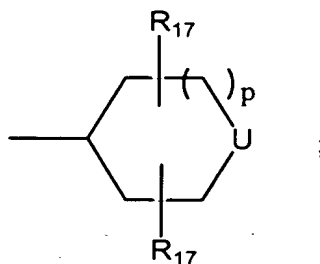


10

wherein Q<sub>4</sub> is



wherein Q<sub>5</sub> is



15

wherein each R<sub>17</sub> is independently H; straight chained

or branched  $C_1$ - $C_7$  alkyl, straight chained or branched  $C_1$ - $C_7$  monofluoroalkyl, straight chained or branched  $C_1$ - $C_7$  polyfluoroalkyl, straight chained or branched  $C_2$ - $C_7$  alkenyl, straight chained or branched  $C_2$ - $C_7$  alkynyl,  $C_5$ - $C_7$  cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_n-O-(CH_2)_m-CH_3$ ;

wherein each  $R_{20}$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl or  $C_5$ - $C_7$  cycloalkenyl; -F, -Cl, -Br, or -I; -NO<sub>2</sub>; -N<sub>3</sub>; -CN; -OR<sub>21</sub>, -OCOR<sub>21</sub>, -COR<sub>21</sub>, -NCOR<sub>21</sub>, -N(R<sub>21</sub>)<sub>2</sub>, -CON(R<sub>21</sub>)<sub>2</sub>, or -COOR<sub>21</sub>; aryl or heteroaryl; or two  $R_{20}$  groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each  $R_{21}$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$  cycloalkenyl or aryl;

wherein each  $R_{22}$  is independently H, F, Cl, or straight chained or branched  $C_1$ - $C_4$  alkyl;

wherein  $q$  is an integer from 2 to 4 inclusive;

wherein each  $m$  is an integer from 0 to 4 inclusive;

30

wherein each  $n$  is an integer from 1 to 4 inclusive;

wherein each p is an integer from 0 to 2 inclusive;

wherein U is O,  $-NR_{16}$ , S,  $C(R_{17})_2$ , or  $-NSO_2R_{16}$ ;

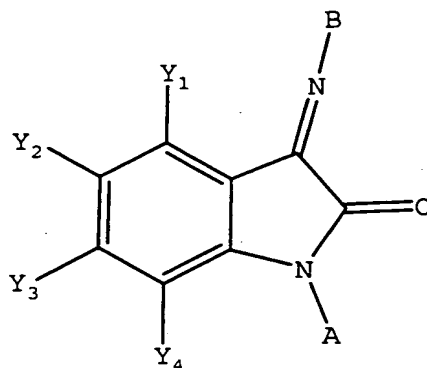
5 wherein Z is  $C_3-C_{10}$  cycloalkyl,  $C_4-C_7$  cyclic ether,  $C_4-C_7$  cyclic thioether, aryl, or heteroaryl;

10 wherein  $R_{16}$  is straight chained or branched  $C_1-C_7$  alkyl, straight chained or branched  $C_1-C_7$  monofluoroalkyl, straight chained or branched  $C_1-C_7$  polyfluoroalkyl, straight chained or branched  $C_2-C_7$  alkenyl, straight chained or branched  $C_2-C_7$  alkynyl,  $C_5-C_7$  cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_q-O-(CH_2)_m-CH_3$ ;

15 wherein B is aryl, or heteroaryl; provided however, if B is aryl or heteroaryl the carbon atom or carbon atoms ortho to the nitrogen atom of the imine bond may only be substituted with one or more of the following -F, -Cl, -Br, -I, -CN, methyl, ethyl or  
20 methoxy;

or a pharmaceutically acceptable salt thereof.

25 The invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound having the structure:

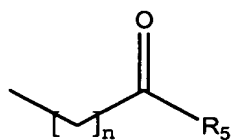


5 wherein each of  $Y_1$ ,  $Y_2$ ,  $Y_3$ , and  $Y_4$  is independently -  
 H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained  
 or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$   
 cycloalkyl, or  $C_5$ - $C_7$  cycloalkenyl; -F, -Cl, -Br, or -  
 I; - $NO_2$ ; - $N_3$ ; -CN; - $OR_4$ , - $SR_4$ , - $OCOR_4$ , - $COR_4$ , - $NCOR_4$ , -  
 10  $N(R_4)_2$ , - $CON(R_4)_2$ , or - $COOR_4$ ; aryl or heteroaryl; or  
 any two of  $Y_1$ ,  $Y_2$ ,  $Y_3$  and  $Y_4$  present on adjacent  
 carbon atoms can constitute a methylenedioxy group;

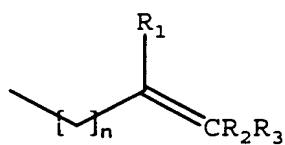
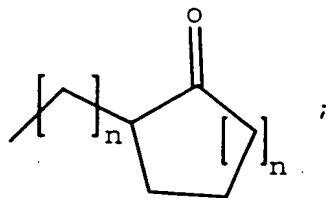
15 wherein each  $R_4$  is independently -H; straight chained  
 or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or  
 polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$   
 alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$   
 cycloalkenyl, aryl or aryl( $C_1$ - $C_6$ )alkyl;

20 wherein A is  $A'$ ,  $Q_3$ ,  $Q_4$ ,  $Q_5$ , straight chained or  
 branched  $C_1$ - $C_7$  alkyl, aryl, heteroaryl, aryl( $C_1$ -  
 $C_6$ )alkyl, heteroaryl( $C_1$ - $C_6$ )alkyl, aryl substituted  
 with an aryl or heteroaryl, heteroaryl substituted  
 with an aryl or heteroaryl; or  $(CHR_{17}) - (CHR_{17})_n - Z$ ;

wherein A' is



;

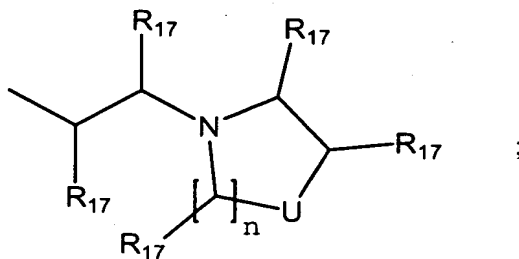


; or



5

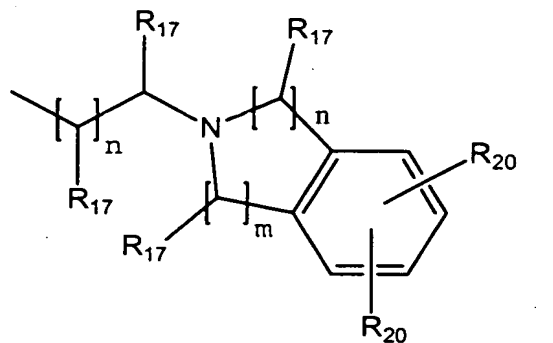
wherein Q<sub>3</sub> is



10

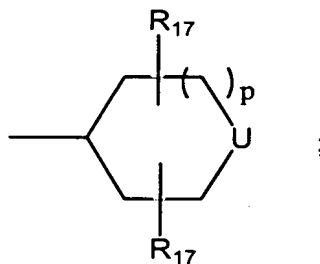
wherein Q<sub>4</sub> is

15



5

wherein  $Q_5$  is



10

wherein  $R_1$  and  $R_2$  are each independently H, straight chained or branched  $C_1$ - $C_7$  alkyl, -F, -Cl, -Br, -I, - $NO_2$ , or -CN;

15

wherein  $R_3$  is H, straight chained or branched  $C_1$ - $C_7$  alkyl, -F, -Cl, -Br, -I, - $NO_2$ , -CN, - $OR_6$ , aryl or heteroaryl;

20

wherein  $R_5$  is straight chained or branched  $C_1$ - $C_7$  alkyl, - $N(R_4)_2$ , - $OR_6$  or aryl;

wherein  $R_6$  is straight chained or branched  $C_1$ - $C_7$  alkyl or aryl;

5            wherein each  $R_{17}$  is independently H; straight chained or branched  $C_1$ - $C_7$  alkyl, straight chained or branched  $C_1$ - $C_7$  monofluoroalkyl, straight chained or branched  $C_1$ - $C_7$  polyfluoroalkyl, straight chained or branched  $C_2$ - $C_7$  alkenyl, straight chained or branched  $C_2$ - $C_7$  alkynyl,  $C_5$ - $C_7$  cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_n-O-(CH_2)_m-CH_3$ ;  
10

          wherein each  $R_{20}$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl or  $C_5$ - $C_7$  cycloalkenyl; -F, -Cl, -Br, or -I; - $NO_2$ ; - $N_3$ ; -CN; - $OR_{21}$ , - $OCOR_{21}$ , - $COR_{21}$ , - $NCOR_{21}$ , - $N(R_{21})_2$ , - $CON(R_{21})_2$ , or - $COOR_{21}$ ; aryl or heteroaryl; or two  $R_{20}$  groups present  
15            on adjacent carbon atoms can join together to form a methylenedioxy group;  
20

          wherein each  $R_{21}$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$  cycloalkenyl, aryl or aryl( $C_1$ - $C_6$ )alkyl;  
25

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

5 wherein each p is an integer from 0 to 2 inclusive;

wherein U is O,  $-NR_{16}$ , S,  $C(R_{17})_2$ , or  $-NSO_2R_{16}$ ;

10 wherein Z is  $C_3-C_{10}$  cycloalkyl,  $C_4-C_7$  cyclic ether,  $C_4-C_7$  cyclic thioether, aryl, or heteroaryl;

15 wherein  $R_{16}$  is straight chained or branched  $C_1-C_7$  alkyl, straight chained or branched  $C_1-C_7$  monofluoroalkyl, straight chained or branched  $C_1-C_7$  polyfluoroalkyl, straight chained or branched  $C_2-C_7$  alkenyl, straight chained or branched  $C_2-C_7$  alkynyl,  $C_5-C_7$  cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_q-O-(CH_2)_m-CH_3$ ;

20 wherein q is an integer from 2 to 4 inclusive;

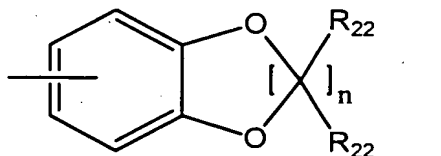
25 wherein B is aryl, heteroaryl, aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl, tricyclic heteroaryl or  $Q_6$ ; provided however, if B is aryl or heteroaryl the carbon atom or carbon atoms ortho to the nitrogen atom of the imine bond may only be substituted with one or more of the following -F, -Cl, -Br, -I, -CN, methyl, ethyl or methoxy;



wherein a tricyclic heteroaryl is a fused three member aromatic system in which one or more of the rings is heteroaryl; carbazole; or acridine;

5

wherein  $Q_6$  is



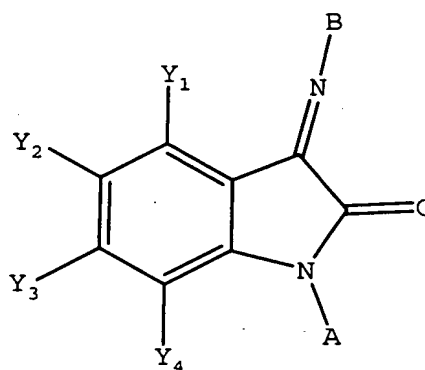
10

wherein each  $R_{22}$  is independently H, F, Cl, or straight chained or branched  $C_1$ - $C_4$  alkyl;

or a pharmaceutically acceptable salt thereof.

15

The invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound having the structure:



20

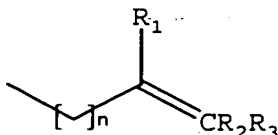
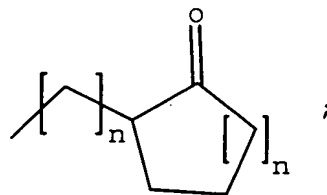
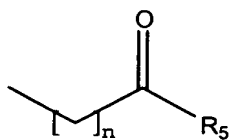
wherein each of  $Y_1$ ,  $Y_2$ ,  $Y_3$ , and  $Y_4$  is independently -

5 H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl, or  $C_5$ - $C_7$  cycloalkenyl; -F, -Cl, -Br, or -I; - $NO_2$ ; - $N_3$ ; -CN; - $OR_4$ , - $SR_4$ , - $OCOR_4$ , - $COR_4$ , - $NCOR_4$ , - $N(R_4)_2$ , - $CON(R_4)_2$ , or - $COOR_4$ ; aryl or heteroaryl; or any two of  $Y_1$ ,  $Y_2$ ,  $Y_3$  and  $Y_4$  present on adjacent carbon atoms can constitute a methylenedioxy group;

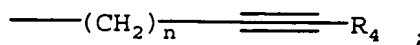
10 wherein each  $R_4$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$  cycloalkenyl, aryl or aryl( $C_1$ - $C_6$ )alkyl;

15 wherein A is A', straight chained or branched  $C_1$ - $C_7$  alkyl, aryl, heteroaryl, aryl( $C_1$ - $C_6$ )alkyl or heteroaryl( $C_1$ - $C_6$ )alkyl;

20 wherein A' is



; or



5            wherein  $R_1$  and  $R_2$  are each independently H, straight  
             chained or branched  $C_1$ - $C_7$  alkyl, -F, -Cl, -Br, -I, -  
              $NO_2$ , or -CN;

             wherein  $R_3$  is H, straight chained or branched  $C_1$ - $C_7$   
10            alkyl, -F, -Cl, -Br, -I, - $NO_2$ , -CN, -OR<sub>6</sub> aryl or  
             heteroaryl;

             wherein  $R_5$  is straight chained or branched  $C_1$ - $C_7$   
             alkyl, -N( $R_4$ )<sub>2</sub>, -OR<sub>6</sub> or aryl;

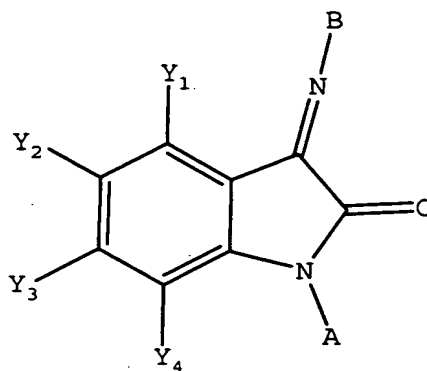
15            wherein  $R_6$  is straight chained or branched  $C_1$ - $C_7$   
             alkyl or aryl;

             wherein B is aryl, or heteroaryl; provided however,  
             if B is aryl or heteroaryl the carbon atom or carbon  
20            atoms ortho to the nitrogen atom of the imine bond  
             may only be substituted with one or more of the  
             following -F, -Cl, -Br, -I, -CN, methyl, ethyl or  
             methoxy;

25            wherein n is an integer from 1 to 4 inclusive;

             or a pharmaceutically acceptable salt thereof.

30            The invention provides a pharmaceutical composition  
             comprising a pharmaceutically acceptable carrier and a  
             compound having the structure:

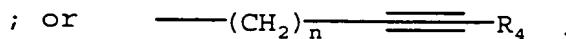
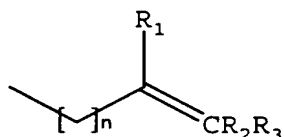
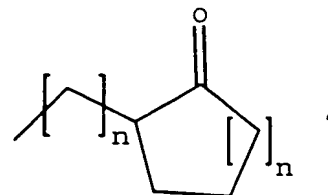
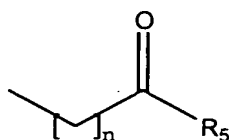


5        wherein each of  $Y_1$ ,  $Y_2$ ,  $Y_3$ , and  $Y_4$  is independently -  
          H; straight chained or branched  $C_1$ - $C_7$  alkyl,  
          monofluoroalkyl or polyfluoroalkyl; straight chained  
 10       or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$   
          cycloalkyl, or  $C_5$ - $C_7$  cycloalkenyl; -F, -Cl, -Br, or -  
          I; - $NO_2$ ; - $N_3$ ; -CN; - $OR_4$ , - $SR_4$ , - $OCOR_4$ , - $COR_4$ , - $NCOR_4$ , -  
           $N(R_4)_2$ , - $CON(R_4)_2$ , or - $COOR_4$ ; aryl or heteroaryl; or  
 15       any two of  $Y_1$ ,  $Y_2$ ,  $Y_3$  and  $Y_4$  present on adjacent  
          carbon atoms can constitute a methylenedioxy group;

15       wherein each  $R_4$  is independently -H; straight chained  
          or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or  
          polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$   
          alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$   
          cycloalkenyl, aryl or aryl( $C_1$ - $C_6$ )alkyl;

20       wherein A is A', straight chained or branched  $C_1$ - $C_7$   
          alkyl, aryl, heteroaryl, aryl( $C_1$ - $C_6$ )alkyl or  
          heteroaryl( $C_1$ - $C_6$ )alkyl;

wherein A' is



5

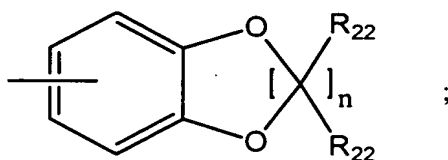
10

wherein B is aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl, tricyclic heteroaryl or Q<sub>6</sub>;

15

wherein a tricyclic heteroaryl is a fused three ring aromatic system in which one or more of the rings is heteroaryl; carbazole; or acridine;

wherein Q<sub>6</sub> is



20

wherein n is an integer from 1 to 4 inclusive;

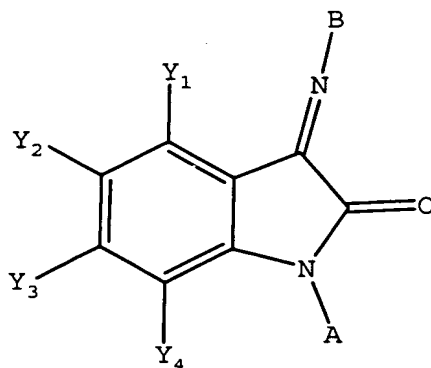
wherein each R<sub>22</sub> is independently H, F,

Cl, or straight chained or branched C<sub>1</sub>-C<sub>4</sub> alkyl;

or a pharmaceutically acceptable salt thereof.

5

The invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound having the structure:



10

wherein each of Y<sub>1</sub>, Y<sub>2</sub>, Y<sub>3</sub>, and Y<sub>4</sub> is independently -H; straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl or alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl, or C<sub>5</sub>-C<sub>7</sub> cycloalkenyl; -F, -Cl, -Br, or -I; -NO<sub>2</sub>; -N<sub>3</sub>; -CN; -OR<sub>4</sub>, -SR<sub>4</sub>, -OCOR<sub>4</sub>, -COR<sub>4</sub>, -NCOR<sub>4</sub>, -N(R<sub>4</sub>)<sub>2</sub>, -CON(R<sub>4</sub>)<sub>2</sub>, or -COOR<sub>4</sub>; aryl or heteroaryl; or any two of Y<sub>1</sub>, Y<sub>2</sub>, Y<sub>3</sub> and Y<sub>4</sub> present on adjacent carbon atoms can constitute a methylenedioxy group;

20

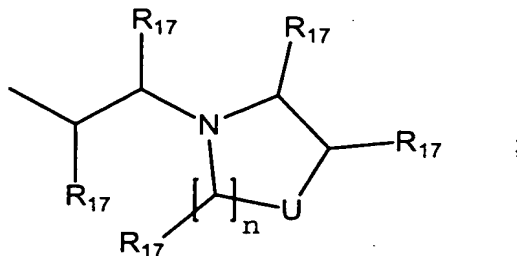
wherein each R<sub>4</sub> is independently -H; straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl or alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>5</sub>-C<sub>7</sub>

25

cycloalkenyl, aryl or aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl;

5 wherein A is Q<sub>3</sub>, Q<sub>4</sub>, Q<sub>5</sub>, aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl, or (CHR<sub>17</sub>)<sub>n</sub>-Z;

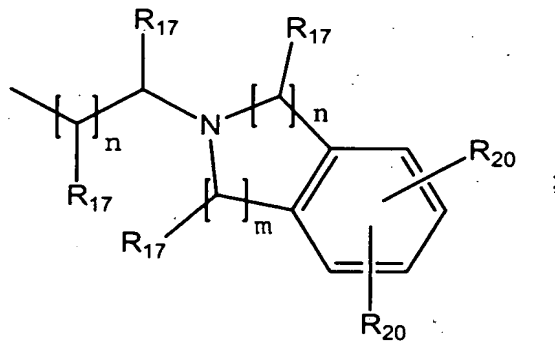
wherein Q<sub>3</sub> is



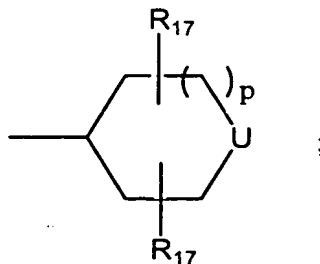
10

15

wherein Q<sub>4</sub> is



wherein Q<sub>5</sub> is



5 wherein each R<sub>17</sub> is independently H; straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> monofluoroalkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> polyfluoroalkyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkynyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, -(CH<sub>2</sub>)<sub>m</sub>-Z, or (CH<sub>2</sub>)<sub>n</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-CH<sub>3</sub>;

wherein each  $R_{20}$  is independently -H; straight  
chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or  
polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$   
15 alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl or  $C_5$ - $C_7$   
cycloalkenyl; -F, -Cl, -Br, or -I; -NO<sub>2</sub>; -N<sub>3</sub>; -CN; -  
OR<sub>21</sub>, -OCOR<sub>21</sub>, -COR<sub>21</sub>, -NCOR<sub>21</sub>, -N(R<sub>21</sub>)<sub>2</sub>, -CON(R<sub>21</sub>)<sub>2</sub>, or  
-COOR<sub>21</sub>; aryl or heteroaryl; or two  $R_{20}$  groups present  
on adjacent carbon atoms can join together to form a  
20 methylenedioxy group;

wherein each  $R_{21}$  is independently -H; straight  
chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or  
polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$   
25 alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$   
cycloalkenyl or aryl;



wherein each  $R_{22}$  is independently H, F, Cl, or straight chained or branched  $C_1$ - $C_4$  alkyl;

wherein q is an integer from 2 to 4 inclusive;

5

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

10

wherein each p is an integer from 0 to 2 inclusive;

wherein U is O,  $-NR_{16}$ , S,  $C(R_{17})_2$ , or  $-NSO_2R_{16}$ ;

15

wherein Z is  $C_3$ - $C_{10}$  cycloalkyl,  $C_4$ - $C_7$  cyclic ether,  $C_4$ - $C_7$  cyclic thioether, aryl, or heteroaryl;

20

wherein  $R_{16}$  is straight chained or branched  $C_1$ - $C_7$  alkyl, straight chained or branched  $C_1$ - $C_7$  monofluoroalkyl, straight chained or branched  $C_1$ - $C_7$  polyfluoroalkyl, straight chained or branched  $C_2$ - $C_7$  alkenyl, straight chained or branched  $C_2$ - $C_7$  alkynyl,  $C_5$ - $C_7$  cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_q-O-(CH_2)_m-CH_3$ ;

25

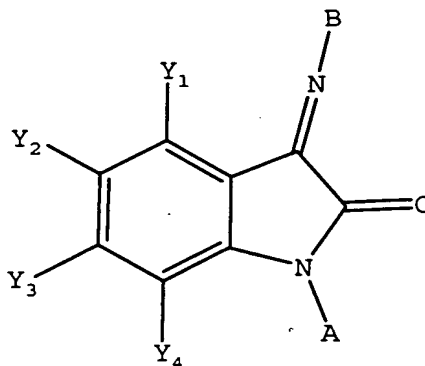
wherein B is aryl, or heteroaryl; provided however, if B is aryl or heteroaryl the carbon atom or carbon atoms ortho to the nitrogen atom of the imine bond may only be substituted with one or more of the following -F, -Cl, -Br, -I, -CN, methyl, ethyl or methoxy;

30

or a pharmaceutically acceptable salt thereof.

5

The invention provides a compound having the structure:



10

15

wherein each of  $Y_1$ ,  $Y_2$ ,  $Y_3$ , and  $Y_4$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl, or  $C_5$ - $C_7$  cycloalkenyl; -F, -Cl, -Br, or -I; - $NO_2$ ; - $N_3$ ; -CN; - $OR_4$ , - $SR_4$ , - $OCOR_4$ , - $COR_4$ , - $NCOR_4$ , - $N(R_4)_2$ , - $CON(R_4)_2$ , or - $COOR_4$ ; aryl or heteroaryl; or any two of  $Y_1$ ,  $Y_2$ ,  $Y_3$  and  $Y_4$  present on adjacent carbon atoms can constitute a methylenedioxy group;

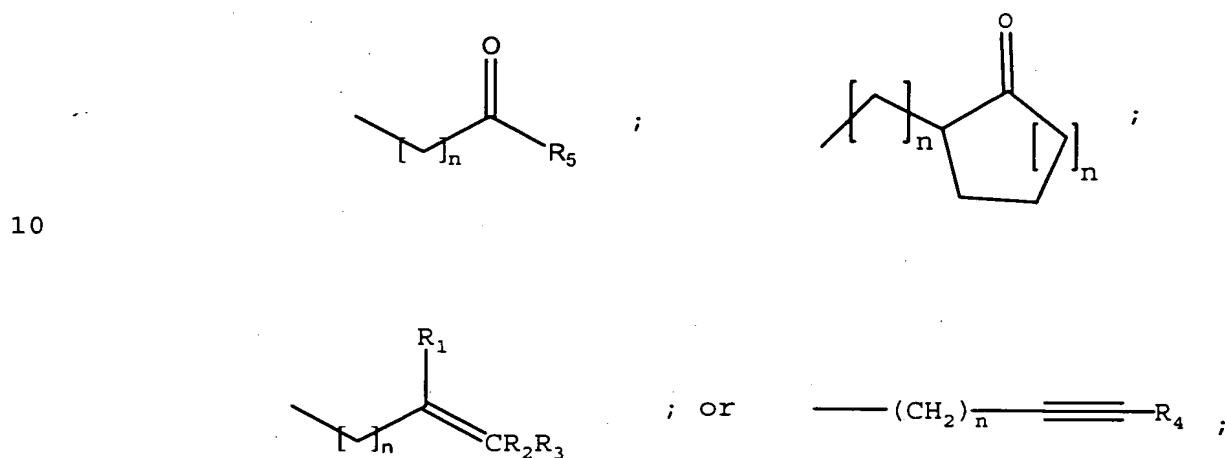
20

wherein each  $R_4$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$

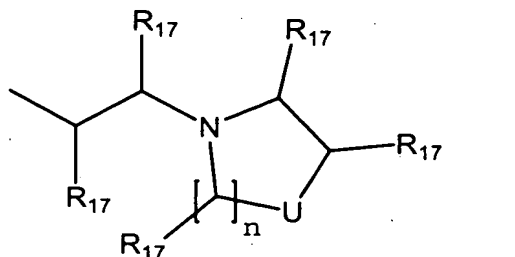
cycloalkenyl, aryl or aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl;

- 5 wherein A is A', Q<sub>3</sub>, Q<sub>4</sub>, Q<sub>5</sub>, straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, aryl, heteroaryl, aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl, heteroaryl(C<sub>1</sub>-C<sub>6</sub>)alkyl, aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl; or (CHR<sub>17</sub>)-(CHR<sub>17</sub>)<sub>n</sub>-Z;

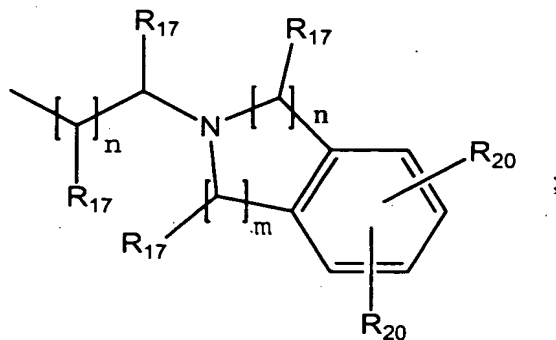
wherein A' is



- 15 wherein Q<sub>3</sub> is



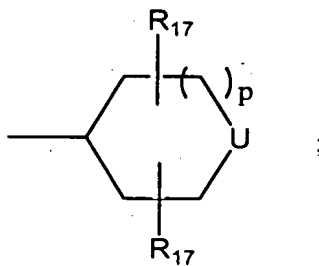
wherein  $Q_4$  is



5

10

wherein  $Q_5$  is



15

wherein  $R_1$  and  $R_2$  are each independently H, straight chained or branched  $C_1$ - $C_7$  alkyl, -F, -Cl, -Br, -I, - $NO_2$ , or -CN;

20

wherein  $R_3$  is H, straight chained or branched  $C_1$ - $C_7$  alkyl, -F, -Cl, -Br, -I, - $NO_2$ , -CN, -OR<sub>6</sub>, aryl or heteroaryl;

wherein  $R_5$  is straight chained or branched  $C_1$ - $C_7$  alkyl,  $-N(R_4)_2$ ,  $-OR_6$  or aryl;

5 wherein  $R_6$  is straight chained or branched  $C_1$ - $C_7$  alkyl or aryl;

10 wherein each  $R_{17}$  is independently H; straight chained or branched  $C_1$ - $C_7$  alkyl, straight chained or branched  $C_1$ - $C_7$  monofluoroalkyl, straight chained or branched  $C_1$ - $C_7$  polyfluoroalkyl, straight chained or branched  $C_2$ - $C_7$  alkenyl, straight chained or branched  $C_2$ - $C_7$  alkynyl,  $C_5$ - $C_7$  cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_n-O-(CH_2)_m-CH_3$ ;

15 wherein each  $R_{20}$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl or  $C_5$ - $C_7$  cycloalkenyl; -F, -Cl, -Br, or -I;  $-NO_2$ ;  $-N_3$ ; -CN; -  
20  $OR_{21}$ ,  $-OCOR_{21}$ ,  $-COR_{21}$ ,  $-NCOR_{21}$ ,  $-N(R_{21})_2$ ,  $-CON(R_{21})_2$ , or  $-COOR_{21}$ ; aryl or heteroaryl; or two  $R_{20}$  groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

25 wherein each  $R_{21}$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$  cycloalkenyl, aryl or aryl( $C_1$ - $C_6$ )alkyl;

30

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

5

wherein each p is an integer from 0 to 2 inclusive;

wherein U is O,  $-NR_{16}$ , S,  $C(R_{17})_2$ , or  $-NSO_2R_{16}$ ;

10 wherein Z is  $C_3$ - $C_{10}$  cycloalkyl,  $C_4$ - $C_7$  cyclic ether,  $C_4$ - $C_7$  cyclic thioether, aryl, or heteroaryl;

wherein  $R_{16}$  is straight chained or branched  $C_1$ - $C_7$  alkyl, straight chained or branched  $C_1$ - $C_7$  monofluoroalkyl, straight chained or branched  $C_1$ - $C_7$  polyfluoroalkyl, straight chained or branched  $C_2$ - $C_7$  alkenyl, straight chained or branched  $C_2$ - $C_7$  alkynyl,  $C_5$ - $C_7$  cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_q-O-(CH_2)_m-CH_3$ ;

15

20 wherein q is an integer from 2 to 4 inclusive;

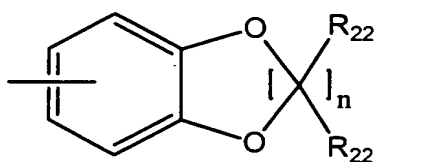
wherein B is aryl, heteroaryl, aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl, tricyclic heteroaryl or  $Q_6$ ; provided however, if B is aryl or heteroaryl the carbon atom or carbon atoms ortho to the nitrogen atom of the imine bond may only be substituted with

25

one or more of the following -F, -Cl, -Br, -I, -CN, methyl, ethyl or methoxy;

5 wherein a tricyclic heteroaryl is a fused three member aromatic system in which one or more of the rings is heteroaryl; carbazole; or acridine;

wherein Q<sub>6</sub> is



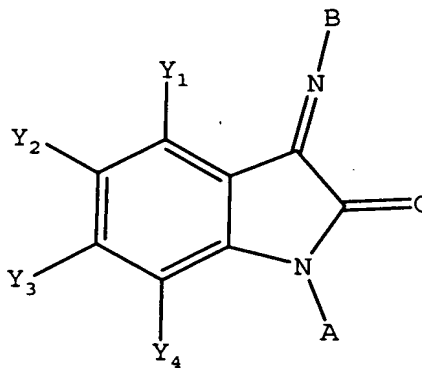
10

wherein each R<sub>22</sub> is independently H, F, Cl, or straight chained or branched C<sub>1</sub>-C<sub>4</sub> alkyl;

or a pharmaceutically acceptable salt thereof.

15

The invention provides a compound having the structure:



20

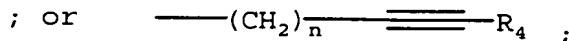
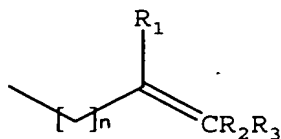
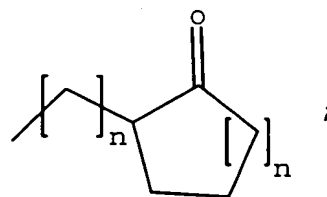
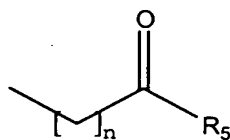
wherein each of Y<sub>1</sub>, Y<sub>2</sub>, Y<sub>3</sub>, and Y<sub>4</sub> is independently - H; straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl,

monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2-C_7$  alkenyl or alkynyl;  $C_3-C_7$  cycloalkyl, or  $C_5-C_7$  cycloalkenyl; -F, -Cl, -Br, or -I; -NO<sub>2</sub>; -N<sub>3</sub>; -CN; -OR<sub>4</sub>, -SR<sub>4</sub>, -OCOR<sub>4</sub>, -COR<sub>4</sub>, -NCOR<sub>4</sub>, -N(R<sub>4</sub>)<sub>2</sub>, -CON(R<sub>4</sub>)<sub>2</sub>, or -COOR<sub>4</sub>; aryl or heteroaryl; or any two of Y<sub>1</sub>, Y<sub>2</sub>, Y<sub>3</sub> and Y<sub>4</sub> present on adjacent carbon atoms can constitute a methylenedioxy group;

wherein each R<sub>4</sub> is independently -H; straight chained or branched  $C_1-C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2-C_7$  alkenyl or alkynyl;  $C_3-C_7$  cycloalkyl,  $C_5-C_7$  cycloalkenyl, aryl or aryl( $C_1-C_6$ )alkyl;

wherein A is A', straight chained or branched  $C_1-C_7$  alkyl, aryl, heteroaryl, aryl( $C_1-C_6$ )alkyl or heteroaryl( $C_1-C_6$ )alkyl;

wherein A' is





wherein  $R_1$  and  $R_2$  are each independently H, straight chained or branched  $C_1$ - $C_7$  alkyl, -F, -Cl, -Br, -I, - $NO_2$ , or -CN;

5

wherein  $R_3$  is H, straight chained or branched  $C_1$ - $C_7$  alkyl, -F, -Cl, -Br, -I, - $NO_2$ , -CN, -OR<sub>6</sub> aryl or heteroaryl;

10

wherein  $R_5$  is straight chained or branched  $C_1$ - $C_7$  alkyl, -N( $R_4$ )<sub>2</sub>, -OR<sub>6</sub> or aryl;

wherein  $R_6$  is straight chained or branched  $C_1$ - $C_7$  alkyl or aryl;

15

wherein B is aryl, or heteroaryl; provided however, if B is aryl or heteroaryl the carbon atom or carbon atoms ortho to the nitrogen atom of the imine bond may only be substituted with one or more of the following -F, -Cl, -Br, -I, -CN, methyl, ethyl or methoxy;

20

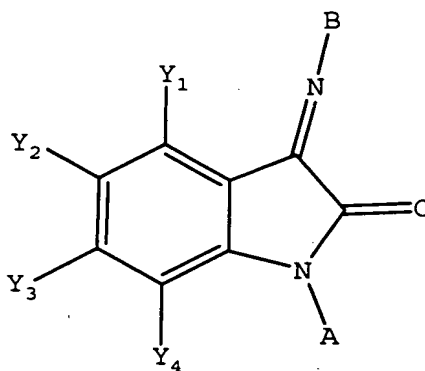
wherein n is an integer from 1 to 4 inclusive;

25

or a pharmaceutically acceptable salt thereof.

30

The invention provides a compound having the structure:

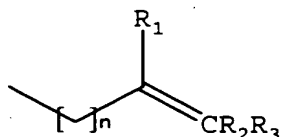
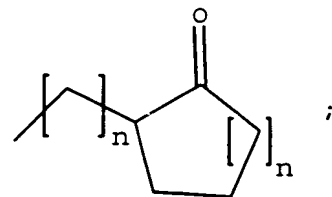
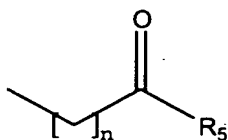


5 wherein each of  $Y_1$ ,  $Y_2$ ,  $Y_3$ , and  $Y_4$  is independently -  
 H; straight chained or branched  $C_1$ - $C_7$  alkyl,  
 monofluoroalkyl or polyfluoroalkyl; straight chained  
 or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$   
 cycloalkyl, or  $C_5$ - $C_7$  cycloalkenyl; -F, -Cl, -Br, or -  
 I; - $NO_2$ ; - $N_3$ ; -CN; - $OR_4$ , - $SR_4$ , - $OCOR_4$ , - $COR_4$ , - $NCOR_4$ , -  
 $N(R_4)_2$ , - $CON(R_4)_2$ , or - $COOR_4$ ; aryl or heteroaryl; or  
 10 any two of  $Y_1$ ,  $Y_2$ ,  $Y_3$  and  $Y_4$  present on adjacent  
 carbon atoms can constitute a methylenedioxy group;

15 wherein each  $R_4$  is independently -H; straight chained  
 or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or  
 polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$   
 alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$   
 cycloalkenyl, aryl or aryl( $C_1$ - $C_6$ )alkyl;

20 wherein A is A', straight chained or branched  $C_1$ - $C_7$   
 alkyl, aryl, heteroaryl, aryl( $C_1$ - $C_6$ )alkyl or  
 heteroaryl( $C_1$ - $C_6$ )alkyl;

wherein A' is



; or



5

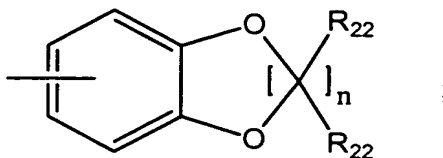
10

wherein B is aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl, tricyclic heteroaryl or Q<sub>6</sub>;

15

wherein a tricyclic heteroaryl is a fused three ring aromatic system in which one or more of the rings is heteroaryl; carbazole; or acridine;

wherein Q<sub>6</sub> is



20

wherein n is an integer from 1 to 4 inclusive;

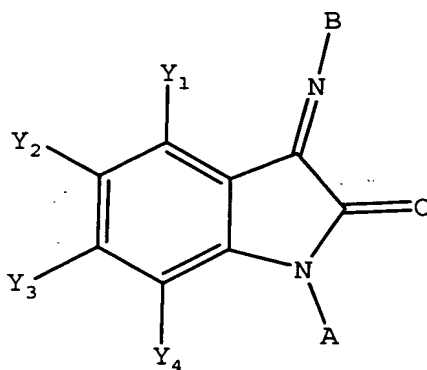
wherein each  $R_{22}$  is independently H, F, Cl, or straight chained or branched  $C_1$ - $C_4$  alkyl;

5

or a pharmaceutically acceptable salt thereof.

10

The invention provides a compound having the structure:



15

wherein each of  $Y_1$ ,  $Y_2$ ,  $Y_3$ , and  $Y_4$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl, or  $C_5$ - $C_7$  cycloalkenyl; -F, -Cl, -Br, or -I; - $NO_2$ ; - $N_3$ ; -CN; - $OR_4$ , - $SR_4$ , - $OCOR_4$ , - $COR_4$ , - $NCOR_4$ , - $N(R_4)_2$ , - $CON(R_4)_2$ , or - $COOR_4$ ; aryl or heteroaryl; or any two of  $Y_1$ ,  $Y_2$ ,  $Y_3$  and  $Y_4$  present on adjacent carbon atoms can constitute a methylenedioxy group;

20

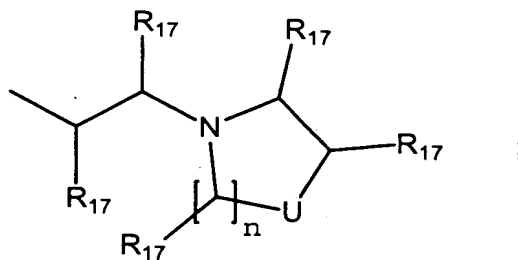
25

wherein each  $R_4$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$

alkenyl or alkynyl;  $C_3-C_7$  cycloalkyl,  $C_5-C_7$  cycloalkenyl, aryl or aryl( $C_1-C_6$ )alkyl;

5 wherein A is  $Q_3$ ,  $Q_4$ ,  $Q_5$ , aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl, or  $(CHR_{17})-(CHR_{17})_n-Z$ ;

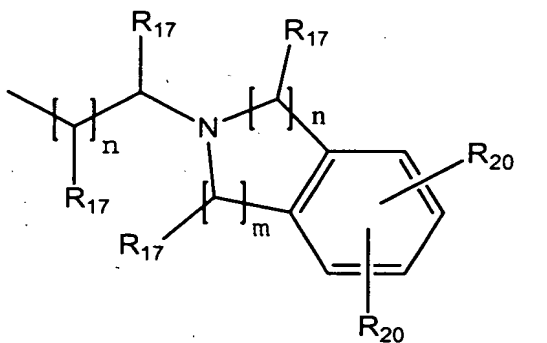
wherein  $Q_3$  is



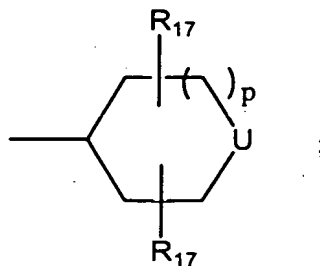
10

15

wherein  $Q_4$  is



wherein  $Q_5$  is



5 wherein each  $R_{17}$  is independently H; straight chained  
 or branched  $C_1$ - $C_7$  alkyl, straight chained or branched  
 $C_1$ - $C_7$  monofluoroalkyl, straight chained or branched  
 $C_1$ - $C_7$  polyfluoroalkyl, straight chained or branched  
 $C_2$ - $C_7$  alkenyl, straight chained or branched  $C_2$ - $C_7$   
 alkynyl,  $C_5$ - $C_7$  cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_n-O-$   
 10  $(CH_2)_m-CH_3$ ;

15 wherein each  $R_{20}$  is independently -H; straight  
 chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or  
 polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$   
 alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl or  $C_5$ - $C_7$   
 cycloalkenyl; -F, -Cl, -Br, or -I;  $-NO_2$ ;  $-N_3$ ; -CN; -  
 $OR_{21}$ ,  $-OCOR_{21}$ ,  $-COR_{21}$ ,  $-NCOR_{21}$ ,  $-N(R_{21})_2$ ,  $-CON(R_{21})_2$ , or  
 $-COOR_{21}$ ; aryl or heteroaryl; or two  $R_{20}$  groups present  
 20 on adjacent carbon atoms can join together to form a  
 methylenedioxy group;

25 wherein each  $R_{21}$  is independently -H; straight  
 chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or  
 polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$   
 alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$   
 cycloalkenyl or aryl;

wherein each  $R_{22}$  is independently H, F, Cl, or straight chained or branched  $C_1$ - $C_4$  alkyl;

wherein q is an integer from 2 to 4 inclusive;

5

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

10

wherein each p is an integer from 0 to 2 inclusive;

wherein U is O,  $-NR_{16}$ , S,  $C(R_{17})_2$ , or  $-NSO_2R_{16}$ ;

15

wherein Z is  $C_3$ - $C_{10}$  cycloalkyl,  $C_4$ - $C_7$  cyclic ether,  $C_4$ - $C_7$  cyclic thioether, aryl, or heteroaryl;

20

wherein  $R_{16}$  is straight chained or branched  $C_1$ - $C_7$  alkyl, straight chained or branched  $C_1$ - $C_7$  monofluoroalkyl, straight chained or branched  $C_1$ - $C_7$  polyfluoroalkyl, straight chained or branched  $C_2$ - $C_7$  alkenyl, straight chained or branched  $C_2$ - $C_7$  alkynyl,  $C_5$ - $C_7$  cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_q-O-(CH_2)_m-CH_3$ ;

25

wherein B is aryl, or heteroaryl; provided however, if B is aryl or heteroaryl the carbon atom or carbon atoms ortho to the nitrogen atom of the imine bond may only be substituted with one or more of the following -F, -Cl, -Br, -I, -CN, methyl, ethyl or methoxy;

30

or a pharmaceutically acceptable salt thereof.

The invention provides a method of treating depression in a subject which comprises administering to the subject a composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a GAL3 receptor antagonist, wherein:

(a) the GAL3 receptor antagonist binds to the human GAL3 receptor with a binding affinity at least ten-fold higher than the binding affinity with which it binds to the human GAL1 receptor;

(b) (1) the GAL3 receptor antagonist does not inhibit the activity of central monoamine oxidase A greater than 50 percent, at a concentration of 10 $\mu$ M; and

(2) the GAL3 receptor antagonist does not inhibit the activity of central monoamine oxidase B greater than 50 percent, at a concentration of 10 $\mu$ M; and

(c) the GAL3 receptor antagonist binds to the human GAL3 receptor with a binding affinity at least ten-fold higher than the binding affinity with which it binds to each of the following transporters: serotonin transporter, norepinephrine transporter, and dopamine transporter.

The invention provides a method of treating anxiety in a subject which comprises administering to the subject a composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a GAL3 receptor antagonist, wherein:

(a) the GAL3 receptor antagonist binds to the human GAL3



receptor with a binding affinity at least ten-fold higher than the binding affinity with which it binds to the human GAL1 receptor; and

- 5 (b) the GAL3 receptor antagonist binds to the human GAL3 receptor with a binding affinity at least ten-fold higher than the binding affinity with which it binds to each of the following transporters: serotonin transporter, norepinephrine transporter, and dopamine transporter.

### Brief Description of the Figures

#### Figure 1: Rat Forced Swim Test Results (Immobility: Normal Rats)

5 Vehicle (V) and test compounds (F10 = fluoxetine at 10 mg/kg ip; C1, C3, C10 or C30 = Example 92 at 1, 3, 10 or 30 mg/kg ip) were injected into normal rats by intraperitoneal administration (n = 5 for each treatment condition). One hour later, rats were examined in a 5  
10 minute forced swim test. For each treatment condition, the number of 5-sec intervals culminating with a display of immobility was derived and plotted as the average +/- S.E.M. A significant decrease in immobility was observed for rats injected with fluoxetine at 10 mg/kg, or with  
15 Example 92 at 3 and 10 mg/kg, relative to vehicle injected controls (p < 0.01, ANOVA and Student-Nerman-Keuls).

#### Figure 2: Rat Forced Swim Test Results (Climbing: Normal Rats)

20 Vehicle (V) and test compounds (F10 = fluoxetine at 10 mg/kg ip; C1, C3, C10 or C30 = Example 92 at 1, 3, 10 or 30 mg/kg ip) were injected into normal rats by intraperitoneal administration (n = 5 for each treatment  
25 condition). One hour later, rats were examined in a 5 minute forced swim test. For each treatment condition, the number of 5-sec intervals culminating with a display of climbing was derived and plotted as the average +/- S.E.M. A significant increase in climbing was observed  
30 for rats injected with Example 92 at 10 mg/kg, relative to vehicle injected controls (p < 0.01, ANOVA and

Student-Nerman-Keuls), but not in rats dosed with Example 92 at 30 mg/kg ip.

Figure 3: Rat Forced Swim Test Results (Swimming: Normal

5 Rats)

Vehicle (V) and test compounds (F10 = fluoxetine at 10 mg/kg ip; C1, C3, C10 or C30 = Example 92 at 1, 3, 10 or 30 mg/kg ip) were injected into normal rats by intraperitoneal administration (n = 5 for each treatment  
10 condition). One hour later, rats were examined in a 5 minute forced swim test. For each treatment condition, the number of 5-sec intervals culminating with a display of swimming was derived and plotted as the average +/- S.E.M. A significant increase in swimming was observed  
15 for rats injected with fluoxetine at 10 mg/kg ip or with Example 92 at 30 mg/kg, relative to vehicle injected controls ( $p < 0.01$ , ANOVA and Student-Nerman-Keuls).

Figure 4: Social Interaction Test Results (Social

20 Interaction: Unfamiliar Rats)

Vehicle (V) and test compounds (CLD 5 = chlordiazepoxide at 5 mg/kg ip; C10, C30 or C100 = Example 92 at 10, 30 or 100 mg/kg ip) were injected into normal rats by intraperitoneal administration (n = 5 for each treatment  
25 condition). One hour later, unfamiliar rats were examined in a 15 minute social interaction test. For each treatment condition, the amount of time spent in social interaction was derived and plotted as the average +/- S.E.M. A significant increase in social interaction was  
30 observed for rats injected with chlordiazepoxide at 5 mg/kg i.p. or with Example 92 at 10 mg/kg ip ( $p < 0.05$ ) as well as 30 mg/kg ( $p < 0.01$ ). When the dose of Example

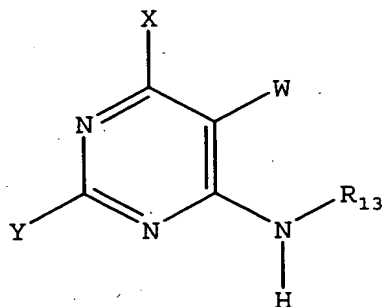
92 was increased to 100 mg/kg, the amount of social interaction time was significantly less than measured after chlordiazepoxide at 5 mg/kg ip or Example 92 at 30 mg/kg ip ( $p < 0.01$ ). Significance in all cases was determined by ANOVA and Student-Nerman-Keuls.

#### Figure 5: Western Blot Results

In order to establish the specificity of the anti-GAL3 antiserum, membranes prepared from COS-7 cells transiently transfected with the rat recombinant GAL3 (Borowsky et al., 1999) (Lane 2) or mock-transfected (vector only) (Lane 3) were applied to an SDS-PAGE gel and blotted using the GAL3 receptor polyclonal antibody. Lane 1 corresponds to molecular weight marker. The anti-GAL3 antiserum labeled proteins in membranes only from rat GAL3-transfected cells (Lane 2); a predominant band was evident with an apparent molecular weight of approximately 56 kDa, (somewhat higher than the amino acid-derived value of 40.4 kDa). The apparently high molecular weight observed for rat GAL3 very likely reflects post-translational processing such as glycosylation; note that rat GAL3 contains multiple N-terminal glycosylation sites (Smith et al., 1998). Relative to the predominant band, additional species of higher molecular weight as well as lower molecular weight were labeled by the GAL3 antiserum. These are interpreted as protein aggregates of C-terminal fragments, as they are absent in mock-transfected cells.

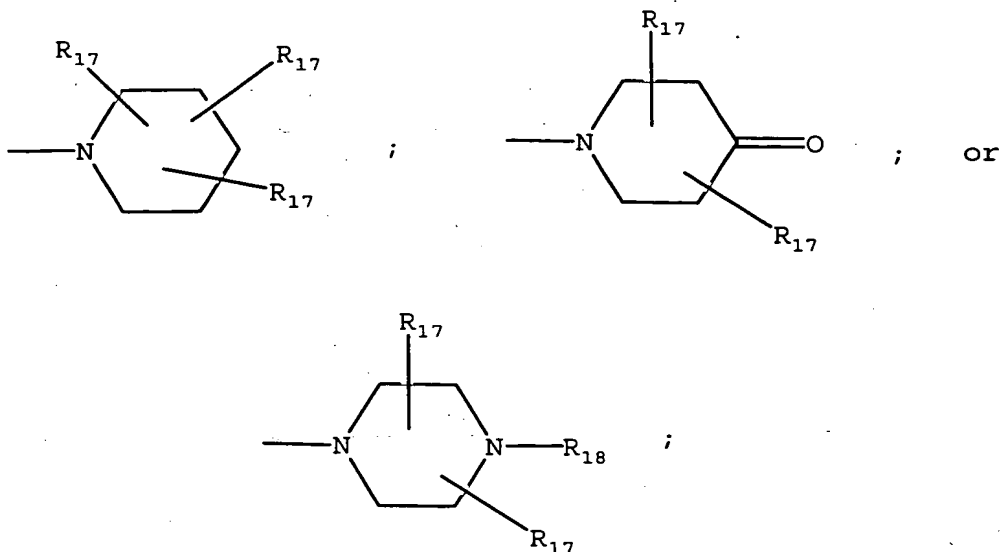
### Detailed Description of the Invention

The present invention provides a method of treating a subject suffering from depression which comprises  
 5 administering to the subject an amount of compound effective to treat the subject's depression wherein the compound has the structure:



wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl,  
 10 propyl, methoxy or ethoxy;

wherein X is;  $\text{NR}_{11}\text{R}_{12}$ ;



wherein  $\text{R}_{11}$  is H, straight chained or branched  $\text{C}_1\text{-C}_7$  alkyl,

$(\text{CH}_2)_q\text{-O-}(\text{CH}_2)_m\text{-CH}_3$ , aryl, or aryl  $(\text{C}_1\text{-C}_6)$ alkyl;

wherein  $\text{R}_{12}$  is straight chained or branched  $\text{C}_1\text{-C}_7$  alkyl,  
 $(\text{CH}_2)_q\text{-O-}(\text{CH}_2)_m\text{-CH}_3$ , or  $-(\text{CH}_2)_m\text{-Z}$ ;

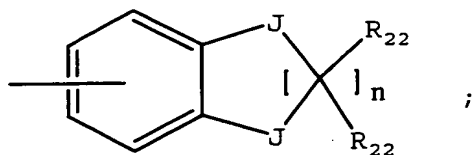
5

wherein  $\text{R}_{13}$  is a bicyclic alkyl ring system, adamantyl, noradamantyl,  $\text{C}_3\text{-C}_{10}$  cycloalkyl, heteroaryl, aryl, aryl $(\text{C}_1\text{-C}_6)$ alkyl,  $\text{Q}_1$  or  $\text{Q}_2$ ;

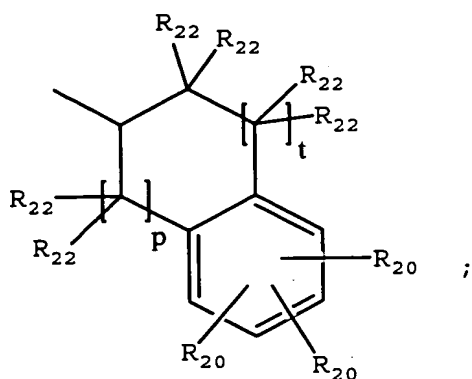
10 wherein aryl may be substituted with one or more  $\text{C}_1\text{-C}_{10}$  straight chained or branched alkyl, aryl, heteroaryl, or  $\text{N}(\text{R}_{19})\text{-Z}$ ;

wherein  $\text{Q}_1$  is

15



wherein  $\text{Q}_2$  is

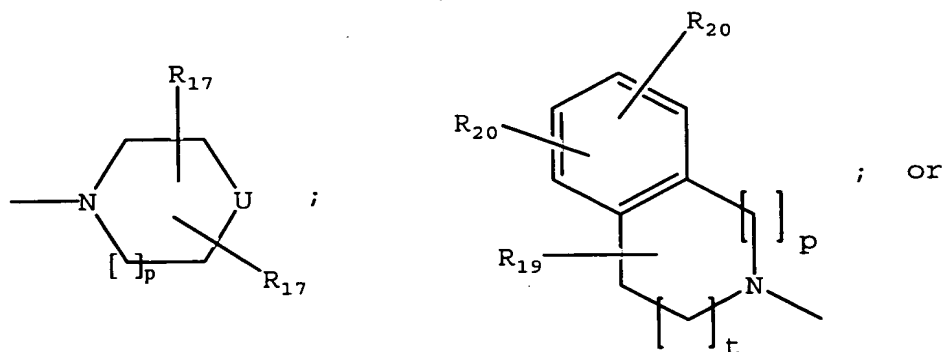


20

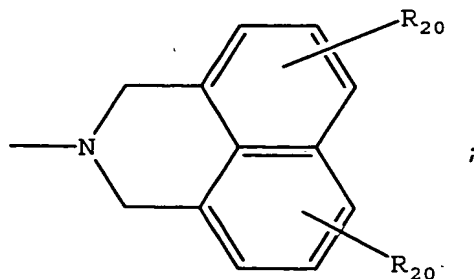
wherein each  $\text{J}$  is independently  $\text{O}$ ,  $\text{S}$ ,  $\text{C}(\text{R}_{22})_2$  or  $\text{NR}_4$ ;

wherein  $R_4$  is H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$  cycloalkenyl or aryl;

wherein Y is  $NR_{14}R_{15}$ ;



10



wherein  $R_{14}$  is H, straight chained or branched  $C_1$ - $C_6$  alkyl,  $(CH_2)_q-O-(CH_2)_m-CH_3$ ,  $C_3$ - $C_6$  cycloalkyl, or  $(C(R_{19})_2)_m-Z$ ;

15

wherein  $R_{15}$  is straight chained or branched  $C_3$ - $C_6$  alkyl,  $(CH_2)_q-O-(CH_2)_m-CH_3$ ,  $C_3$ - $C_6$  cycloalkyl,  $(C(R_{19})_2)_mN(R_{16})_2$  or  $(C(R_{19})_2)_m-Z$ ;

20 wherein  $R_{16}$  is straight chained or branched  $C_1$ - $C_7$  alkyl,

straight chained or branched  $C_1-C_7$  monofluoroalkyl,  
 straight chained or branched  $C_1-C_7$  polyfluoroalkyl,  
 straight chained or branched  $C_2-C_7$  alkenyl, straight  
 chained or branched  $C_2-C_7$  alkynyl,  $C_5-C_7$  cycloalkenyl, -  
 5  $(CH_2)_m-Z$ , or  $(CH_2)_q-O-(CH_2)_m-CH_3$ ;

wherein each  $R_{17}$  is independently H;  $-OR_{21}$ ,  $-OCOR_{21}$ ,  $-COR_{21}$ ,  
 $-NCOR_{21}$ ,  $-N(R_{21})_2$ ,  $-CON(R_{21})_2$ ,  $-COOR_{21}$ , straight chained or  
 branched  $C_1-C_7$  alkyl, straight chained or branched  $C_1-C_7$   
 10 monofluoroalkyl, straight chained or branched  $C_1-C_7$   
 polyfluoroalkyl, straight chained or branched  $C_2-C_7$   
 alkenyl, straight chained or branched  $C_2-C_7$  alkynyl,  $C_5-C_7$   
 cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_n-O-(CH_2)_m-CH_3$ ;

15 wherein  $R_{18}$  is straight chained or branched  $C_1-C_6$  alkyl, -  
 $(CH_2)_m-Z$ , or  $(CH_2)_q-O-(CH_2)_m-CH_3$ ;

wherein each  $R_{19}$  is independently H, or straight chained  
 or branched  $C_1-C_6$  alkyl;

20

wherein each  $R_{20}$  is independently -H; straight chained or  
 branched  $C_1-C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl;  
 straight chained or branched  $C_2-C_7$  alkenyl or alkynyl;  $C_3-$   
 $C_7$  cycloalkyl or  $C_5-C_7$  cycloalkenyl; -F, -Cl, -Br, or -I;  
 25  $-NO_2$ ;  $-N_3$ ;  $-CN$ ;  $-OR_{21}$ ,  $-OCOR_{21}$ ,  $-COR_{21}$ ,  $-NCOR_{21}$ ,  $-N(R_{21})_2$ , -  
 $CON(R_{21})_2$ , or  $-COOR_{21}$ ; aryl or heteroaryl; or two  $R_{20}$  groups  
 present on adjacent carbon atoms can join together to  
 form a methylenedioxy group;

30 wherein each  $R_{21}$  is independently -H; straight chained or  
 branched  $C_1-C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl;  
 straight chained or branched  $C_2-C_7$  alkenyl or alkynyl;  $C_3-$



C<sub>7</sub> cycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, aryl, or aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl;

wherein each R<sub>22</sub> is independently H, F, Cl or C<sub>1</sub>-C<sub>4</sub>  
5 straight chained or branched alkyl;

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

10

wherein p is an integer from 0 to 2 inclusive;

wherein q is an integer from 2 to 4 inclusive;

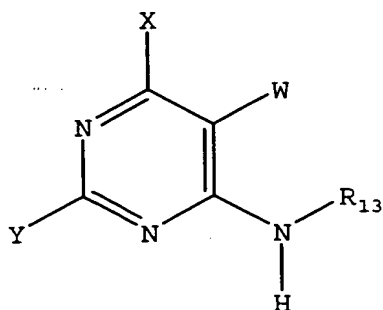
15 wherein t is 1 or 2;

wherein U is O, -NR<sub>16</sub>, S, C(R<sub>17</sub>)<sub>2</sub>, or -NSO<sub>2</sub>R<sub>16</sub>;

wherein Z is C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>4</sub>-C<sub>7</sub> cyclic ether, C<sub>4</sub>-C<sub>7</sub>  
20 cyclic thioether, aryl, or heteroaryl; or

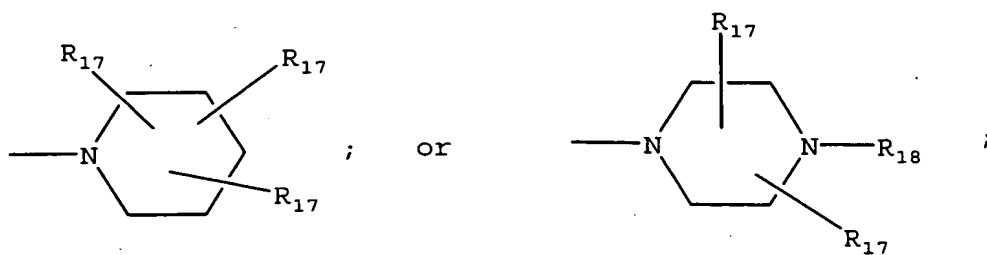
a pharmaceutically acceptable salt thereof.

25 The invention provides a method of treating a subject suffering from depression which comprises administering to the subject an amount of compound effective to treat the subject's depression wherein the compound has the structure:



wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

5 wherein X is  $\text{NR}_{11}\text{R}_{12}$ ;



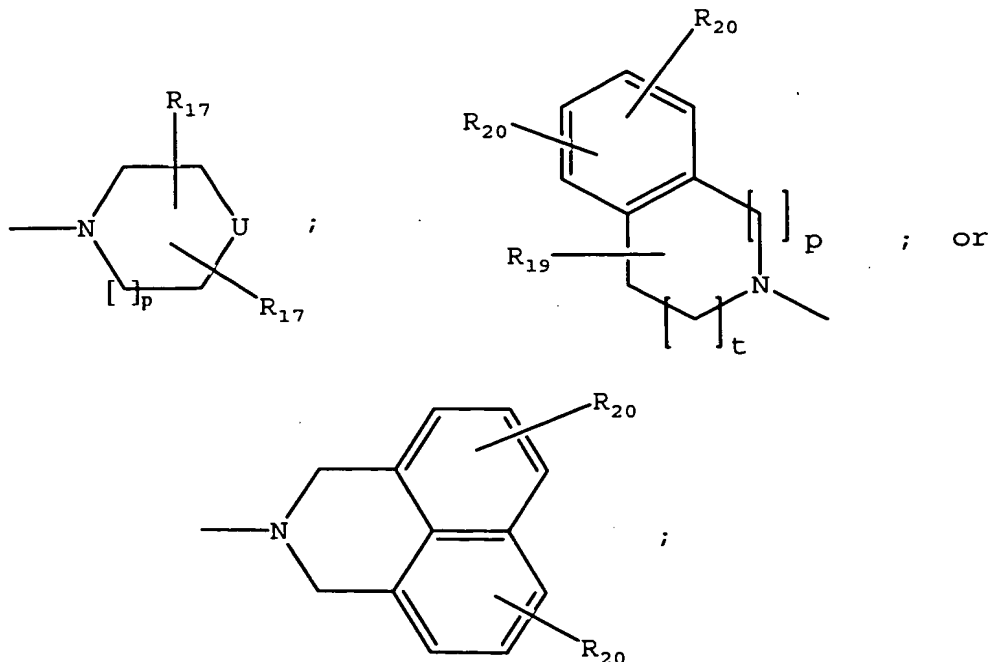
wherein  $\text{R}_{11}$  is H, straight chained or branched  $\text{C}_1\text{-C}_7$  alkyl,  $(\text{CH}_2)_q\text{-O-(CH}_2)_m\text{-CH}_3$ , aryl or aryl( $\text{C}_1\text{-C}_6$ )alkyl;

10 wherein  $\text{R}_{12}$  is straight chained or branched  $\text{C}_1\text{-C}_7$  alkyl,  $(\text{CH}_2)_q\text{-O-(CH}_2)_m\text{-CH}_3$ , or  $-(\text{CH}_2)_m\text{-Z}$ ;

wherein  $\text{R}_{13}$  is a bicyclic alkyl ring system, aryl or aryl( $\text{C}_1\text{-C}_6$ )alkyl;

15

wherein Y is  $\text{NR}_{14}\text{R}_{15}$ ;



wherein  $R_{14}$  is H, straight chained or branched  $C_1$ - $C_6$  alkyl,  $(CH_2)_q$ -O- $(CH_2)_m$ -CH<sub>3</sub>,  $C_3$ - $C_6$  cycloalkyl, or  $(C(R_{19})_2)_m$ -Z;

5

wherein  $R_{15}$  is straight chained or branched  $C_3$ - $C_6$  alkyl,  $(CH_2)_q$ -O- $(CH_2)_m$ -CH<sub>3</sub>,  $C_3$ - $C_6$  cycloalkyl, or  $(C(R_{19})_2)_m$ -Z;

wherein U is O, -NR<sub>16</sub>, S, C( $R_{17}$ )<sub>2</sub>, or -NSO<sub>2</sub>R<sub>16</sub>;

10

wherein Z is  $C_3$ - $C_{10}$  cycloalkyl, aryl, or heteroaryl;

wherein  $R_{16}$  is straight chained or branched  $C_1$ - $C_7$  alkyl, straight chained or branched  $C_1$ - $C_7$  monofluoroalkyl, straight chained or branched  $C_1$ - $C_7$  polyfluoroalkyl, straight chained or branched  $C_2$ - $C_7$  alkenyl, straight chained or branched  $C_2$ - $C_7$  alkynyl,  $C_5$ - $C_7$  cycloalkenyl, - $(CH_2)_m$ -Z, or  $(CH_2)_q$ -O- $(CH_2)_m$ -CH<sub>3</sub>;

15

wherein each  $R_{17}$  is independently H;  $-OR_{21}$ ,  $-OCOR_{21}$ ,  $-COR_{21}$ ,  $-NCOR_{21}$ ,  $-N(R_{21})_2$ ,  $-CON(R_{21})_2$ ,  $-COOR_{21}$ , straight chained or branched  $C_1$ - $C_7$  alkyl, straight chained or branched  $C_1$ - $C_7$  monofluoroalkyl, straight chained or branched  $C_1$ - $C_7$  polyfluoroalkyl, straight chained or branched  $C_2$ - $C_7$  alkenyl, straight chained or branched  $C_2$ - $C_7$  alkynyl,  $C_5$ - $C_7$  cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_n-O-(CH_2)_m-CH_3$ ;

wherein  $R_{18}$  is straight chained or branched  $C_1$ - $C_6$  alkyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_q-O-(CH_2)_m-CH_3$ ;

wherein each  $R_{19}$  is independently H, or straight chained or branched  $C_1$ - $C_6$  alkyl;

wherein each  $R_{20}$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl or  $C_5$ - $C_7$  cycloalkenyl; -F, -Cl, -Br, or -I;  $-NO_2$ ;  $-N_3$ ; -CN;  $-OR_{21}$ ,  $-OCOR_{21}$ ,  $-COR_{21}$ ,  $-NCOR_{21}$ ,  $-N(R_{21})_2$ ,  $-CON(R_{21})_2$ , or  $-COOR_{21}$ ; aryl or heteroaryl; or two  $R_{20}$  groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each  $R_{21}$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$  cycloalkenyl, aryl or aryl( $C_1$ - $C_6$ )alkyl;

wherein each  $m$  is an integer from 0 to 4 inclusive;

wherein each  $n$  is an integer from 1 to 4 inclusive;

wherein p is an integer from 0 to 2 inclusive;

wherein q is an integer from 2 to 4 inclusive;

5

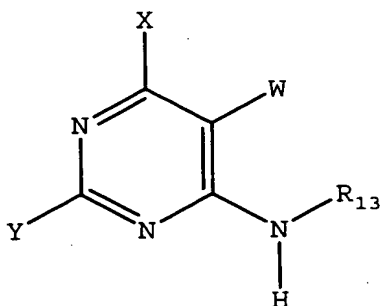
wherein t is 1 or 2; or

a pharmaceutically acceptable salt thereof.

10

The invention provides a method of treating a subject suffering from depression which comprises administering to the subject an amount of compound effective to treat the subject's depression wherein the compound has the structure:

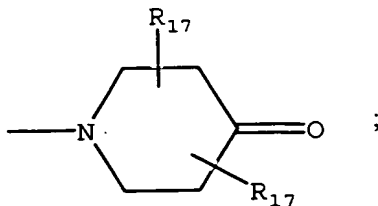
15



wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

20

wherein X is N(CH<sub>3</sub>)<sub>2</sub> or

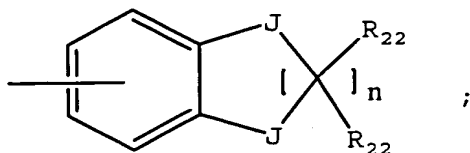


wherein  $R_{13}$  is an aryl, adamantyl, noradamantyl,  $C_3$ - $C_{10}$  cycloalkyl, heteroaryl,  $Q_1$  or  $Q_2$ ;

5

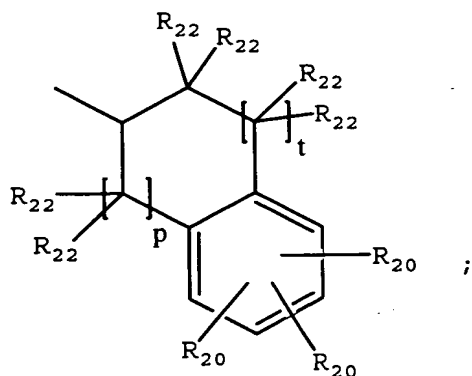
wherein aryl may be substituted with one or more  $C_1$ - $C_{10}$  straight chained or branched alkyl, aryl, heteroaryl, or  $N(R_{19})-Z$ ;

10 wherein  $Q_1$  is



wherein  $Q_2$  is

15

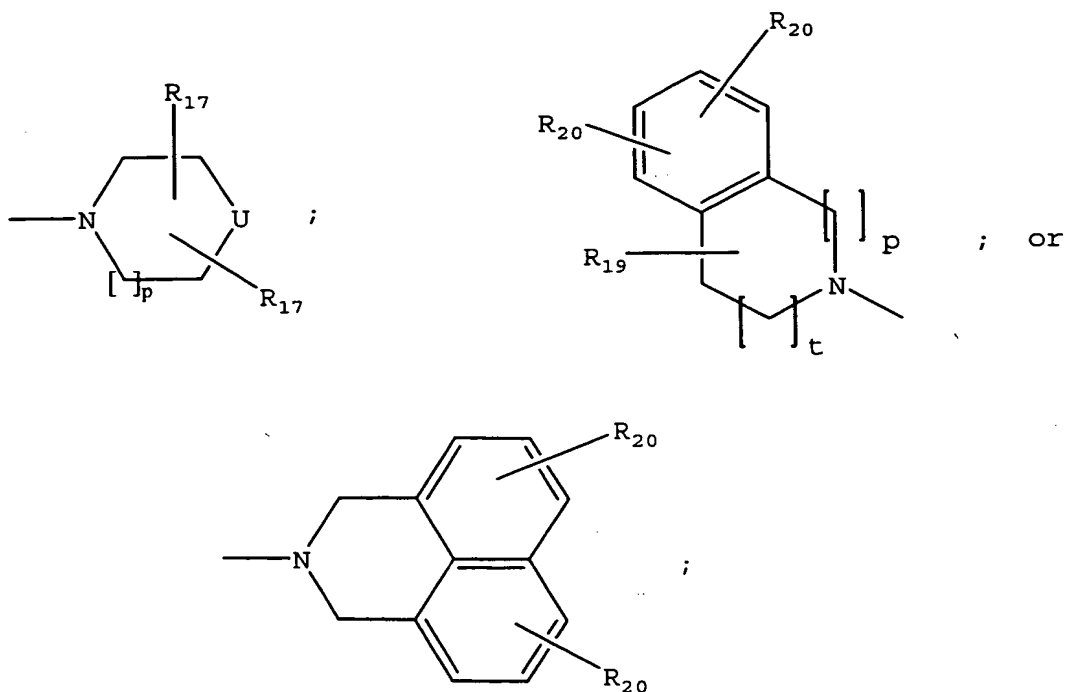


wherein each J is independently O, S,  $C(R_{22})_2$  or  $NR_4$ ;

wherein  $R_4$  is -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$  cycloalkenyl or aryl;

5

wherein Y is  $NR_{14}R_{15}$ ;



- 10 wherein  $R_{14}$  is H, straight chained or branched  $C_1$ - $C_6$  alkyl,  $(CH_2)_q$ -O- $(CH_2)_m$ -CH<sub>3</sub>,  $C_3$ - $C_6$  cycloalkyl, or  $(C(R_{19})_2)_m$ -Z;

wherein  $R_{15}$  is straight chained or branched  $C_3$ - $C_6$  alkyl,  $(CH_2)_q$ -O- $(CH_2)_m$ -CH<sub>3</sub>,  $C_3$ - $C_6$  cycloalkyl, or  $(C(R_{19})_2)_m$ -Z;

15

wherein U is O,  $-NR_{16}$ , S,  $C(R_{17})_2$ , or  $-NSO_2R_{16}$ ;

wherein Z is  $C_3$ - $C_{10}$  cycloalkyl, aryl, or heteroaryl;

wherein  $R_{16}$  is straight chained or branched  $C_1$ - $C_7$  alkyl,  
 straight chained or branched  $C_1$ - $C_7$  monofluoroalkyl,  
 straight chained or branched  $C_1$ - $C_7$  polyfluoroalkyl,  
 5 straight chained or branched  $C_2$ - $C_7$  alkenyl, straight  
 chained or branched  $C_2$ - $C_7$  alkynyl,  $C_5$ - $C_7$  cycloalkenyl, -  
 $(CH_2)_m-Z$ , or  $(CH_2)_q-O-(CH_2)_m-CH_3$ ;

wherein each  $R_{17}$  is independently H;  $-OR_{21}$ ,  $-OCOR_{21}$ ,  $-COR_{21}$ ,  
 10  $-NCOR_{21}$ ,  $-N(R_{21})_2$ ,  $-CON(R_{21})_2$ ,  $-COOR_{21}$ , straight chained or  
 branched  $C_1$ - $C_7$  alkyl, straight chained or branched  $C_1$ - $C_7$   
 monofluoroalkyl, straight chained or branched  $C_1$ - $C_7$   
 polyfluoroalkyl, straight chained or branched  $C_2$ - $C_7$   
 alkenyl, straight chained or branched  $C_2$ - $C_7$  alkynyl,  $C_5$ - $C_7$   
 15 cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_n-O-(CH_2)_m-CH_3$ ;

wherein  $R_{18}$  is straight chained or branched  $C_1$ - $C_6$  alkyl, -  
 $(CH_2)_m-Z$ , or  $(CH_2)_q-O-(CH_2)_m-CH_3$ ;

20 wherein each  $R_{19}$  is independently H, or straight chained  
 or branched  $C_1$ - $C_6$  alkyl;

wherein each  $R_{20}$  is independently -H; straight chained or  
 branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl;  
 25 straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ -  
 $C_7$  cycloalkyl or  $C_5$ - $C_7$  cycloalkenyl; -F, -Cl, -Br, or -I;  
 $-NO_2$ ;  $-N_3$ ; -CN;  $-OR_{21}$ ,  $-OCOR_{21}$ ,  $-COR_{21}$ ,  $-NCOR_{21}$ ,  $-N(R_{21})_2$ , -  
 $CON(R_{21})_2$ , or  $-COOR_{21}$ ; aryl or heteroaryl; or two  $R_{20}$  groups  
 present on adjacent carbon atoms can join together to  
 30 form a methylenedioxy group;

wherein each  $R_{21}$  is independently -H; straight chained or



branched C<sub>1</sub>-C<sub>7</sub> alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl or alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, aryl or aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl;

5 wherein each R<sub>22</sub> is independently H, F, Cl or C<sub>1</sub>-C<sub>4</sub> straight chained or branched alkyl;

wherein each m is an integer from 0 to 4 inclusive;

10 wherein each n is an integer from 1 to 4 inclusive;

wherein p is an integer from 0 to 2 inclusive;

15 wherein q is an integer from 2 to 4 inclusive;

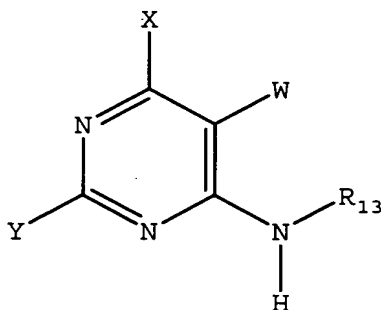
wherein t is 1 or 2; or

a pharmaceutically acceptable salt thereof.

20

The invention provides a method of treating a subject suffering from depression which comprises administering to the subject an amount of compound effective to treat the subject's depression wherein the compound has the

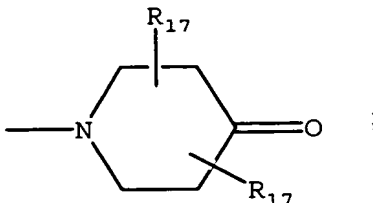
25 structure:



wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl,

propyl, methoxy or ethoxy;

wherein X is  $N(CH_3)_2$  or



5

wherein  $R_{13}$  is a bicyclic alkyl ring system, aryl or aryl( $C_1$ - $C_6$ )alkyl;

10 wherein Y is  $NR_{14}R_{15}$ ;

wherein  $R_{14}$  is H, straight chained or branched  $C_1$ - $C_6$  alkyl,  $(CH_2)_q$ -O- $(CH_2)_m$ - $CH_3$ ,  $C_3$ - $C_6$  cycloalkyl, or  $(C(R_{19})_2)_m$ -Z;

15 wherein  $R_{15}$  is  $(C(R_{19})_2)_m$ - $N(R_{16})_2$ ;

wherein Z is  $C_3$ - $C_{10}$  cycloalkyl, aryl, or heteroaryl;

20 wherein  $R_{16}$  is straight chained or branched  $C_1$ - $C_7$  alkyl, straight chained or branched  $C_1$ - $C_7$  monofluoroalkyl, straight chained or branched  $C_1$ - $C_7$  polyfluoroalkyl, straight chained or branched  $C_2$ - $C_7$  alkenyl, straight chained or branched  $C_2$ - $C_7$  alkynyl,  $C_5$ - $C_7$  cycloalkenyl,  $(CH_2)_m$ -Z, or  $(CH_2)_q$ -O- $(CH_2)_m$ - $CH_3$ ;

25

wherein each  $R_{17}$  is independently H;  $-OR_{21}$ ,  $-OCOR_{21}$ ,  $-COR_{21}$ ,  $-NCOR_{21}$ ,  $-N(R_{21})_2$ ,  $-CON(R_{21})_2$ ,  $-COOR_{21}$ , straight chained or branched  $C_1$ - $C_7$  alkyl, straight chained or branched  $C_1$ - $C_7$  monofluoroalkyl, straight chained or branched  $C_1$ - $C_7$

polyfluoroalkyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkynyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, -(CH<sub>2</sub>)<sub>m</sub>-Z, or (CH<sub>2</sub>)<sub>n</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-CH<sub>3</sub>;

5 wherein each R<sub>19</sub> is independently H, or straight chained or branched C<sub>1</sub>-C<sub>6</sub> alkyl;

wherein each R<sub>21</sub> is independently -H; straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, monofluoroalkyl or polyfluoroalkyl;  
 10 straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl or alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, aryl or aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl;

wherein each m is an integer from 0 to 4 inclusive;

15

wherein each n is an integer from 1 to 4 inclusive;

wherein q is an integer from 2 to 4 inclusive; or

20 a pharmaceutically acceptable salt thereof.

As used in the present invention, the term "bicyclic alkyl ring systems" includes, but is not limited to, bicyclo[2.2.1]heptane, bicyclo[3.1.1]heptane and  
 25 bicyclo[2.2.2]octane. In addition, the bicyclic alkyl ring systems may be substituted with one or more of the following: -F, -NO<sub>2</sub>, -CN, straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> monofluoroalkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> polyfluoroalkyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub>  
 30 alkenyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkynyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, -N(R<sub>21</sub>)<sub>2</sub>, -OR<sub>21</sub>, -COR<sub>21</sub>, -

$\text{CO}_2\text{R}_{21}$ ,  $-\text{CON}(\text{R}_{21})_2$  or  $(\text{CH}_2)_n\text{-O-}(\text{CH}_2)_m\text{-CH}_3$ .

As used in the present invention, the term "cycloalkyl" includes,  $\text{C}_3\text{-C}_7$  cycloalkyl moieties which may be substituted with one or more of the following: -F,  $-\text{NO}_2$ , -CN, straight chained or branched  $\text{C}_1\text{-C}_7$  alkyl, straight chained or branched  $\text{C}_1\text{-C}_7$  monofluoroalkyl, straight chained or branched  $\text{C}_1\text{-C}_7$  polyfluoroalkyl, straight chained or branched  $\text{C}_2\text{-C}_7$  alkenyl, straight chained or branched  $\text{C}_2\text{-C}_7$  alkynyl,  $\text{C}_3\text{-C}_7$  cycloalkyl,  $\text{C}_3\text{-C}_7$  monofluorocycloalkyl,  $\text{C}_3\text{-C}_7$  polyfluorocycloalkyl,  $\text{C}_5\text{-C}_7$  cycloalkenyl,  $-\text{N}(\text{R}_4)_2$ ,  $-\text{OR}_4$ ,  $-\text{COR}_4$ ,  $-\text{NCOR}_4$ ,  $-\text{CO}_2\text{R}_4$ ,  $-\text{CON}(\text{R}_4)_2$  or  $(\text{CH}_2)_n\text{-O-}(\text{CH}_2)_m\text{-CH}_3$ .

As used in the present invention, the term "cyclohexyl" includes, cyclohexyl groups which may be substituted with one or more of the following: -F,  $-\text{NO}_2$ , -CN, straight chained or branched  $\text{C}_1\text{-C}_7$  alkyl, straight chained or branched  $\text{C}_1\text{-C}_7$  monofluoroalkyl, straight chained or branched  $\text{C}_1\text{-C}_7$  polyfluoroalkyl, straight chained or branched  $\text{C}_2\text{-C}_7$  alkenyl, straight chained or branched  $\text{C}_2\text{-C}_7$  alkynyl,  $\text{C}_3\text{-C}_7$  cycloalkyl,  $\text{C}_3\text{-C}_7$  monofluorocycloalkyl,  $\text{C}_3\text{-C}_7$  polyfluorocycloalkyl,  $\text{C}_5\text{-C}_7$  cycloalkenyl,  $-\text{N}(\text{R}_4)_2$ ,  $-\text{OR}_4$ ,  $-\text{COR}_4$ ,  $-\text{NCOR}_4$ ,  $-\text{CO}_2\text{R}_4$ ,  $-\text{CON}(\text{R}_4)_2$  or  $(\text{CH}_2)_n\text{-O-}(\text{CH}_2)_m\text{-CH}_3$ .

25

As used in the present invention, the term "cycloalkenyl" includes,  $\text{C}_5\text{-C}_7$  cycloalkenyl moieties which may be substituted with one or more of the following: -F, -Cl, -Br, -I,  $-\text{NO}_2$ , -CN, straight chained or branched  $\text{C}_1\text{-C}_7$  alkyl, straight chained or branched  $\text{C}_1\text{-C}_7$  monofluoroalkyl, straight chained or branched  $\text{C}_1\text{-C}_7$  polyfluoroalkyl, straight chained or branched  $\text{C}_2\text{-C}_7$  alkenyl, straight

chained or branched C<sub>2</sub>-C<sub>7</sub> alkynyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>3</sub>-C<sub>7</sub> monofluorocycloalkyl, C<sub>3</sub>-C<sub>7</sub> polyfluorocycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, -N(R<sub>4</sub>)<sub>2</sub>, -OR<sub>4</sub>, -COR<sub>4</sub>, -NCOR<sub>4</sub>, -CO<sub>2</sub>R<sub>4</sub>, -CON(R<sub>4</sub>)<sub>2</sub> or (CH<sub>2</sub>)<sub>n</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-CH<sub>3</sub>.

5

In the present invention, the term "heteroaryl" is used to include five and six membered unsaturated rings that may contain one or more oxygen, sulfur, or nitrogen atoms. Examples of heteroaryl groups include, but are not limited to, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, and triazinyl.

15

In addition the term "heteroaryl" is used to include fused bicyclic ring systems that may contain one or more heteroatoms such as oxygen, sulfur and nitrogen. Examples of such heteroaryl groups include, but are not limited to, indolizinyl, indolyl, isoindolyl, benzo[b]furanyl, benzo[b]thiophenyl, indazolyl, benzimidazolyl, purinyl, benzoxazolyl, benzisoxazolyl, benzo[b]thiazolyl, imidazo[2,1-b]thiazolyl, cinnolinyl, quinazolinyl, quinoxalinyl, 1,8-naphthyridinyl, pteridinyl, quinolinyl, isoquinolinyl, phthalimidyl and 2,1,3-benzothiazolyl.

25

The term "heteroaryl" also includes those chemical moieties recited above which may be substituted with one or more of the following: -F, -Cl, -Br, -I, -NO<sub>2</sub>, -CN, straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> monofluoroalkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> polyfluoroalkyl, straight chained or

30

branched C<sub>2</sub>-C<sub>7</sub> alkenyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkynyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>3</sub>-C<sub>7</sub> monofluorocycloalkyl, C<sub>3</sub>-C<sub>7</sub> polyfluorocycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, -N(R<sub>4</sub>)<sub>2</sub>, -OR<sub>4</sub>, -COR<sub>4</sub>, -NCOR<sub>4</sub>, -CO<sub>2</sub>R<sub>4</sub>, -CON(R<sub>4</sub>)<sub>2</sub> or (CH<sub>2</sub>)<sub>n</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-CH<sub>3</sub>.

5

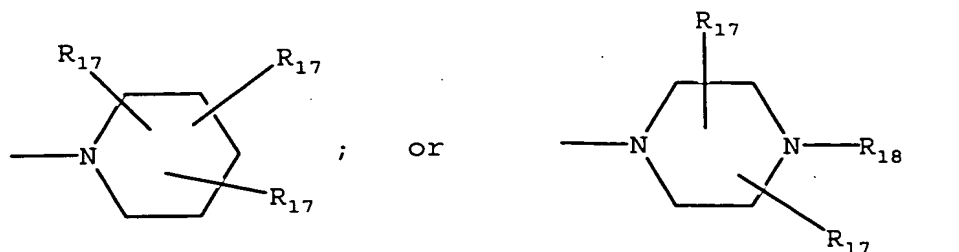
The term "heteroaryl" further includes the N-oxides of those chemical moieties recited above which include at least one nitrogen atom.

10 In the present invention the term "aryl" is phenyl or naphthyl. The term "aryl" also includes phenyl and naphthyl which may be substituted with one or more of the following: -F, -Cl, -Br, -I, -NO<sub>2</sub>, -CN, straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> monofluoroalkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> polyfluoroalkyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkynyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>3</sub>-C<sub>7</sub> monofluorocycloalkyl, C<sub>3</sub>-C<sub>7</sub> polyfluorocycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, -N(R<sub>4</sub>)<sub>2</sub>, -OR<sub>4</sub>, -SR<sub>4</sub>, -OCOR<sub>4</sub>, -COR<sub>4</sub>, -NCOR<sub>4</sub>, -CO<sub>2</sub>R<sub>4</sub>, -CON(R<sub>4</sub>)<sub>2</sub> or (CH<sub>2</sub>)<sub>n</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-CH<sub>3</sub>.

25 In one embodiment of any of the methods described herein, the compound is enantiomerically and diasteriomERICALLY pure. In one embodiment, the compound is enantiomerically or diasteriomERICALLY pure.

30 In one embodiment of any of the methods described herein, the compound can be administered orally.

In one embodiment, X is:

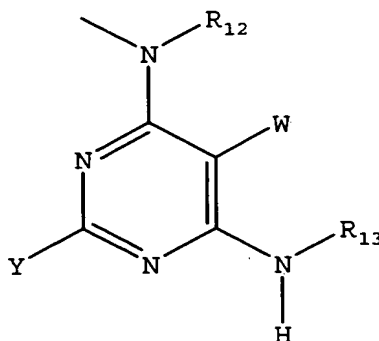


5

In one embodiment, X is  $\text{NR}_{11}\text{R}_{12}$  and  $\text{R}_{11}$  is H or straight chained or branched  $\text{C}_1\text{-C}_7$  alkyl.

In one embodiment, the compound has the structure:

10



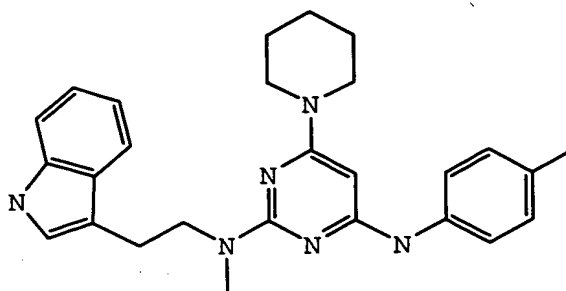
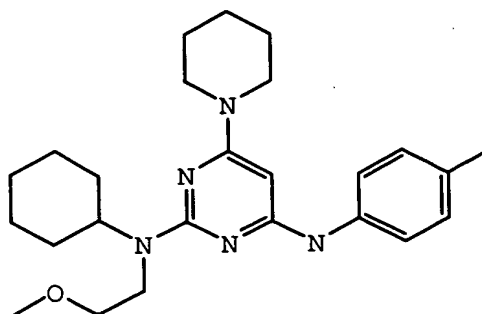
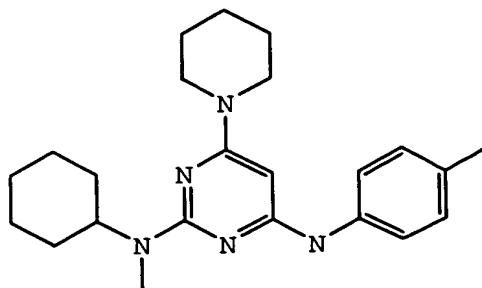
In one embodiment,  $\text{R}_{13}$  is a bicyclic alkyl ring system, cyclohexyl or aryl.

15

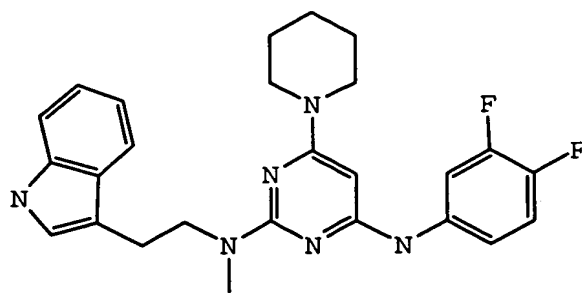
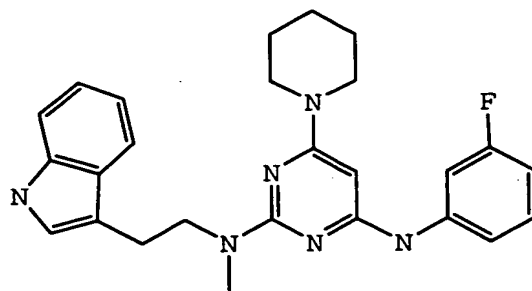
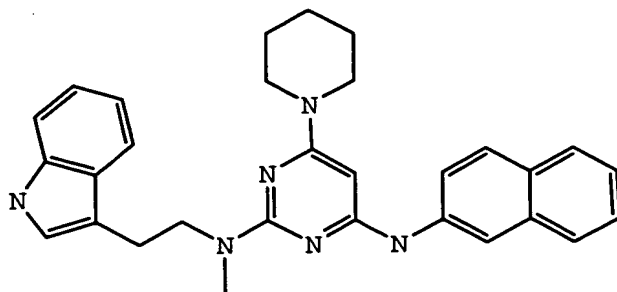
In one embodiment,  $\text{R}_{14}$  is H, straight chained or branched  $\text{C}_1\text{-C}_6$  alkyl or  $(\text{CH}_2)_q\text{-O-(CH}_2)_m\text{-CH}_3$ .

In one embodiment,  $\text{R}_{14}$  is H, straight chained or branched  
20  $\text{C}_1\text{-C}_6$  alkyl or  $(\text{CH}_2)_q\text{-O-(CH}_2)_m\text{-CH}_3$ .

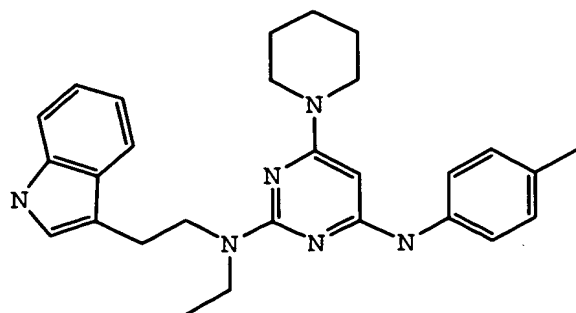
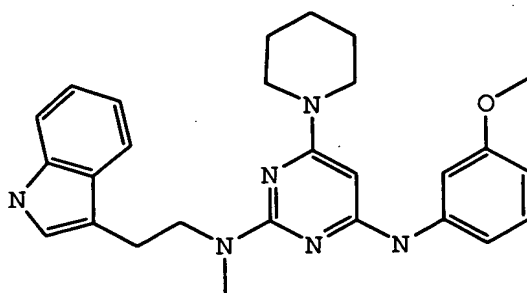
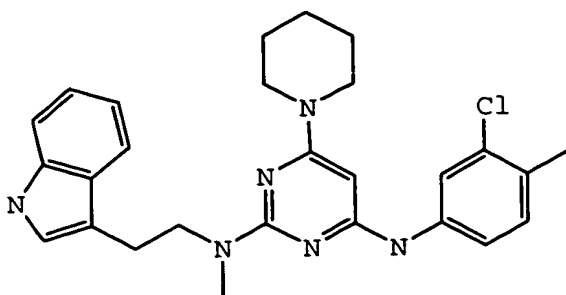
In one embodiment, the compound is selected from the group consisting of:

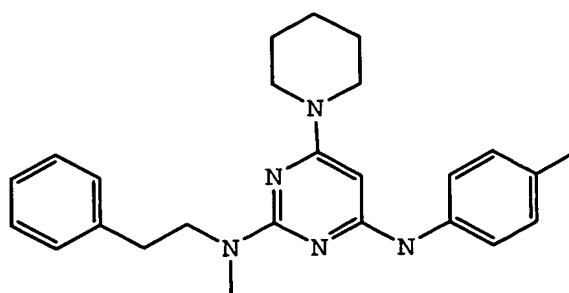
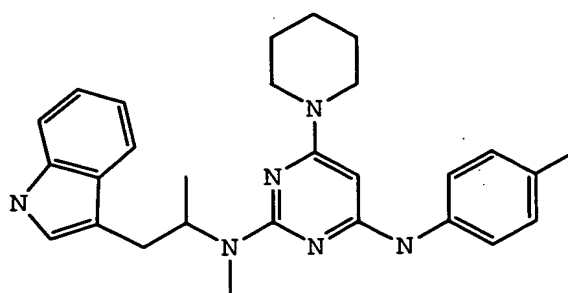
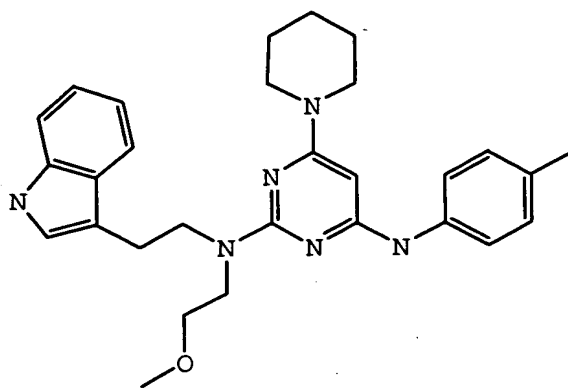






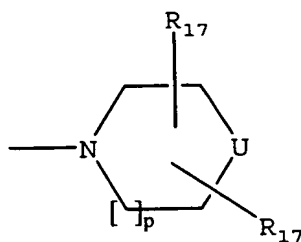
151





5

In one embodiment, Y is

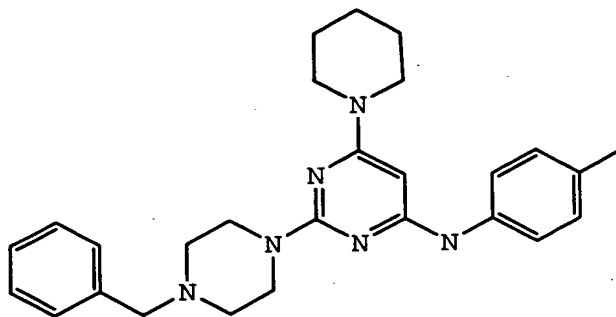


In one embodiment, U is  $\text{NR}_{16}$ .

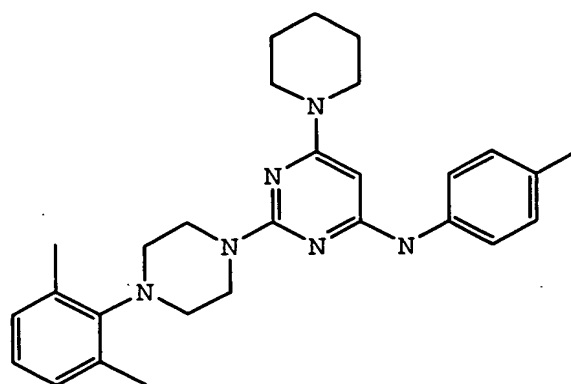
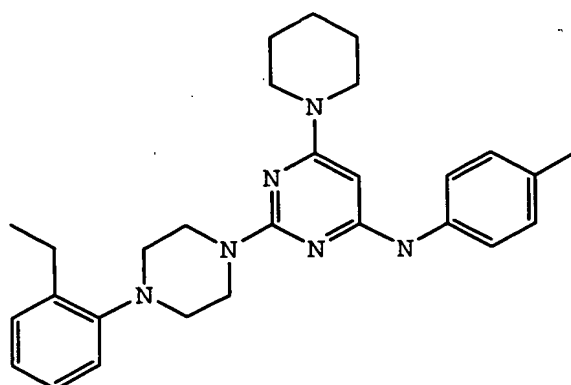
5 In one embodiment,  $\text{R}_{16}$  is  $(\text{CH}_2)_m\text{-Z}$ .

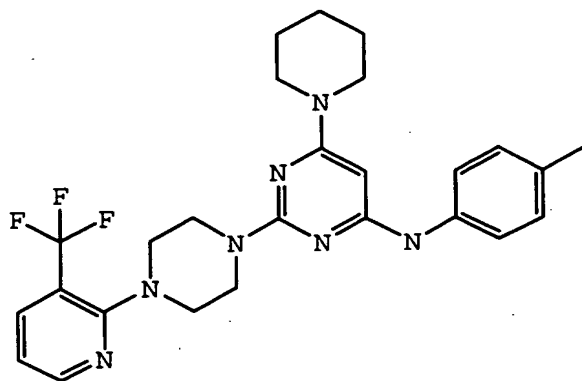
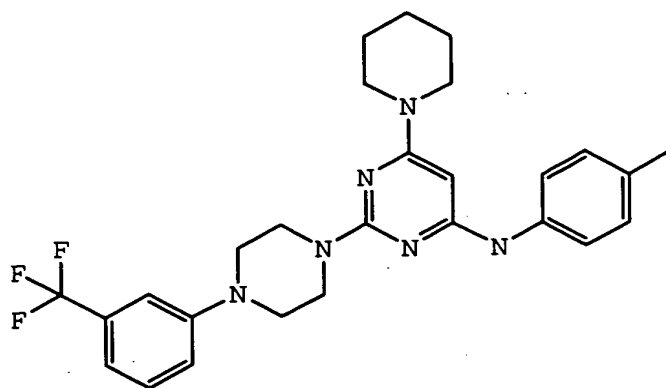
In one embodiment, Z is aryl or heteroaryl.

In one embodiment, the compound is selected from the  
10 group consisting of:

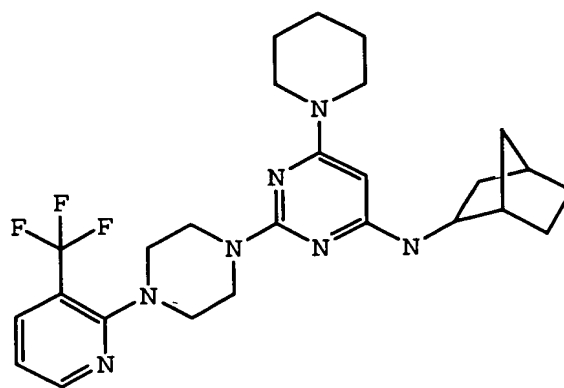


154

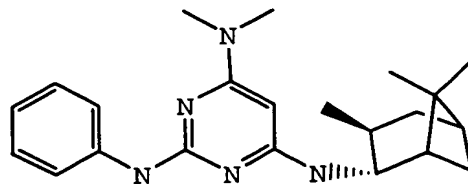
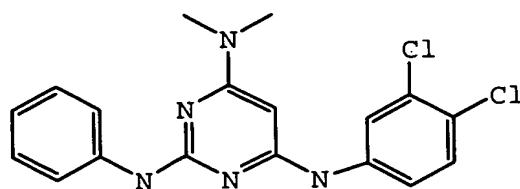
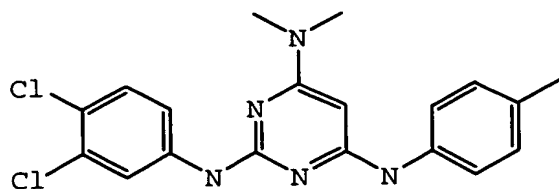


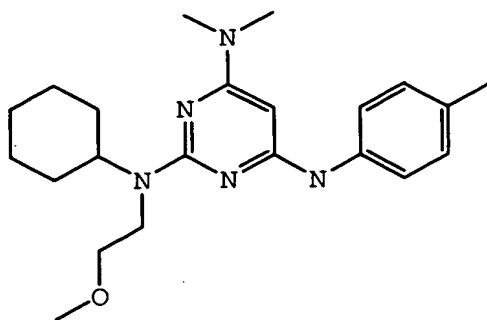


; and

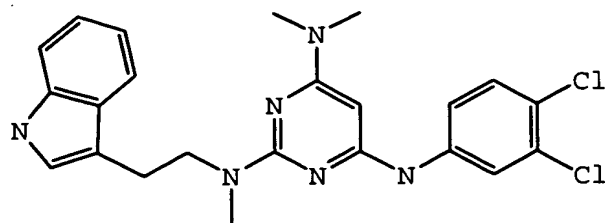
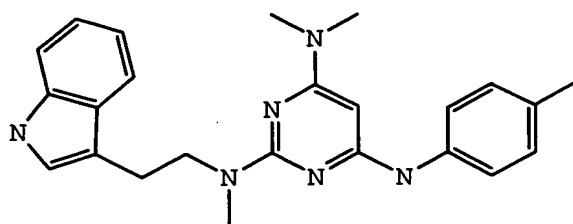


In one embodiment, the compound is selected from the group consisting of:



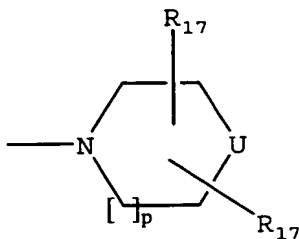


; and



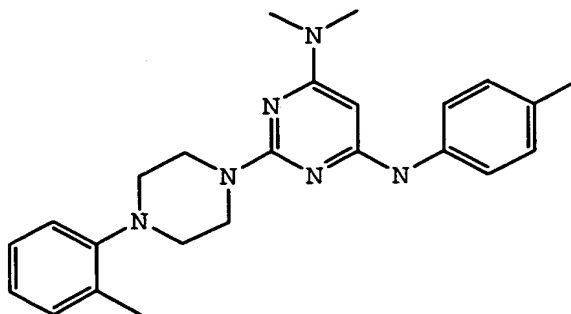


In one embodiment, Y is

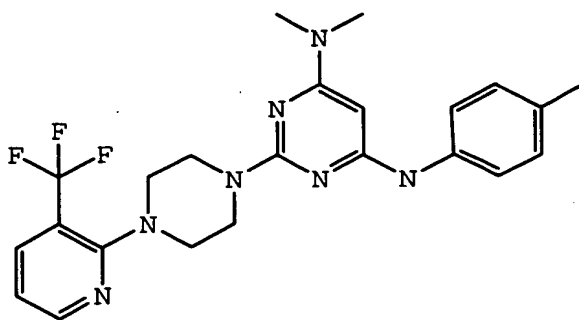


5 In one embodiment, U is  $\text{NR}_{16}$ .

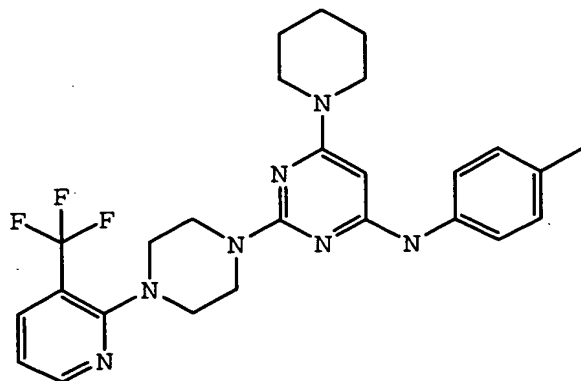
In one embodiment, the compound is



; or

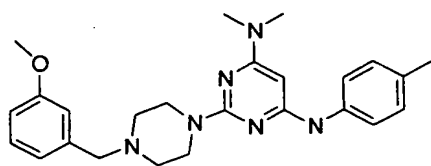


In one embodiment, the compound is

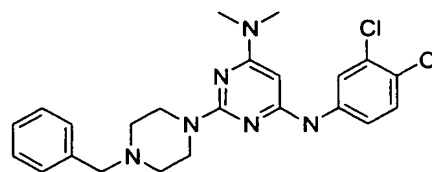


5

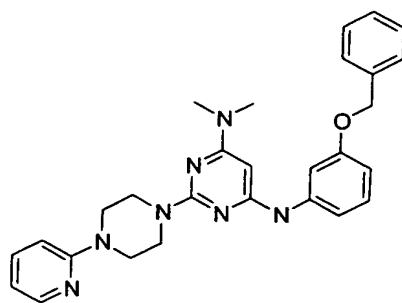
In one embodiment, the compound is selected from the  
10 group consisting of:



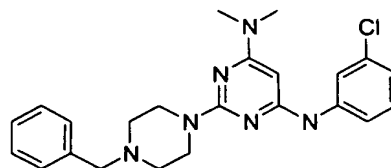
;



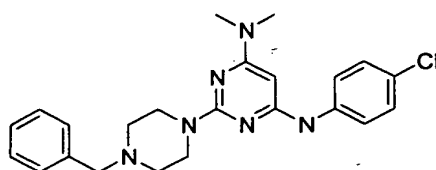
;



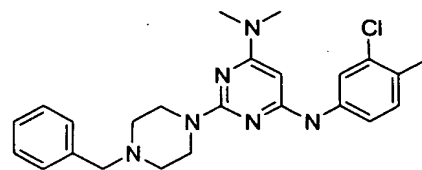
;



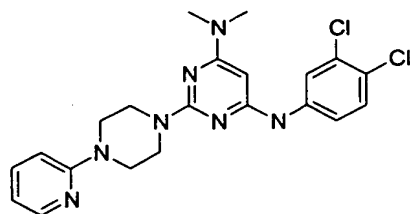
;



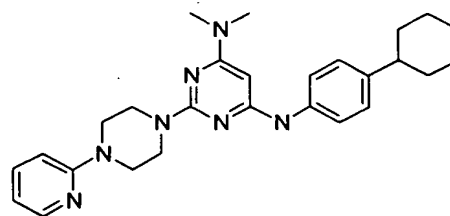
;



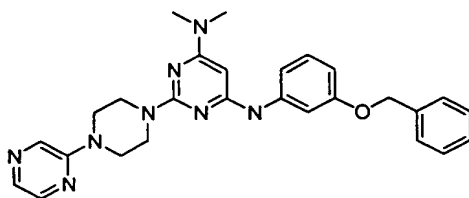
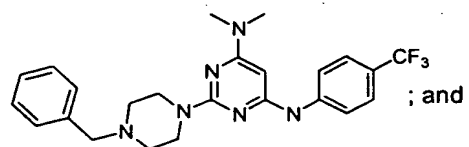
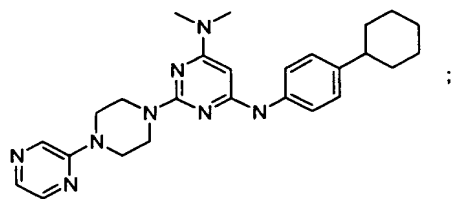
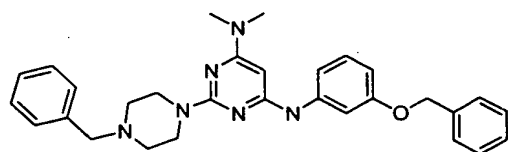
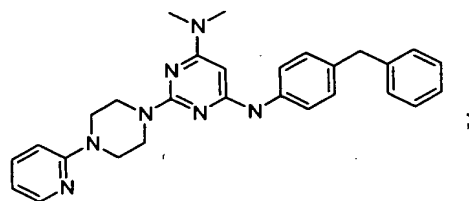
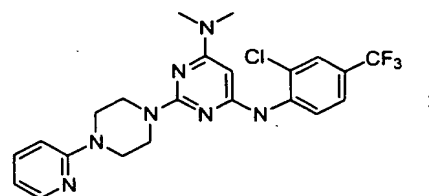
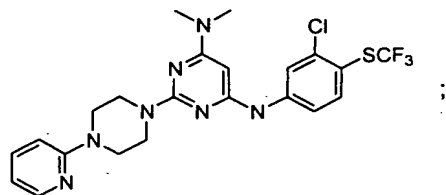
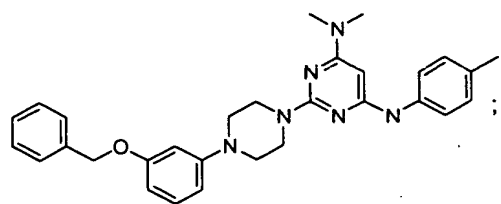
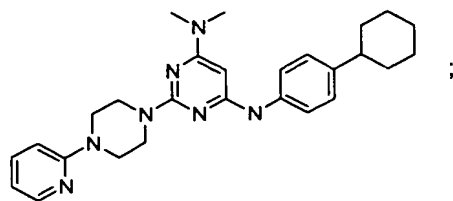
;



; and



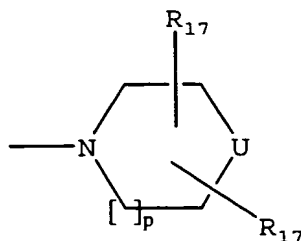
- 5 In one embodiment, the compound is selected from the group consisting of:



In one embodiment, X is  $N(CH_3)_2$ .

5

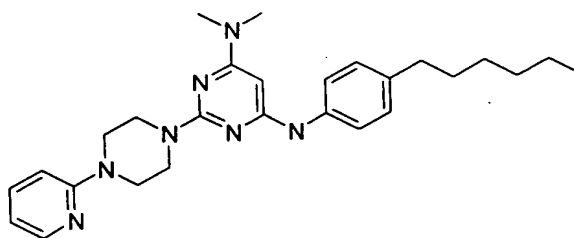
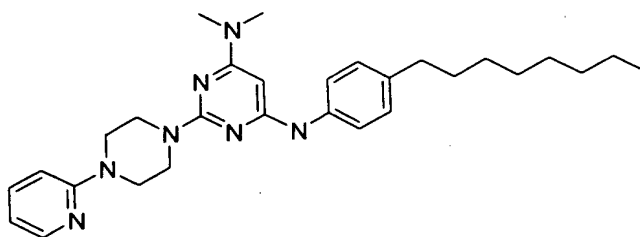
In one embodiment, Y is



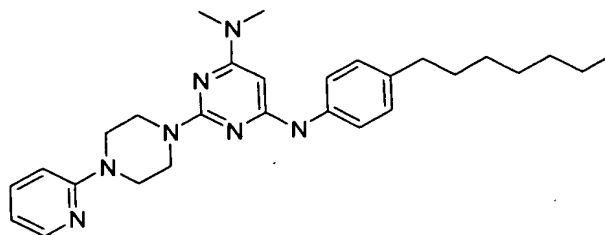
In one embodiment,  $R_{13}$  is an aryl substituted with a  $C_1$ - $C_{10}$  straight chained alkyl.

5

In one embodiment, the compound is selected from a group consisting of:

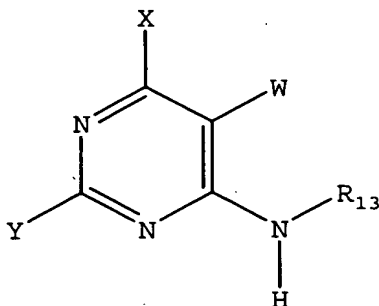


; and



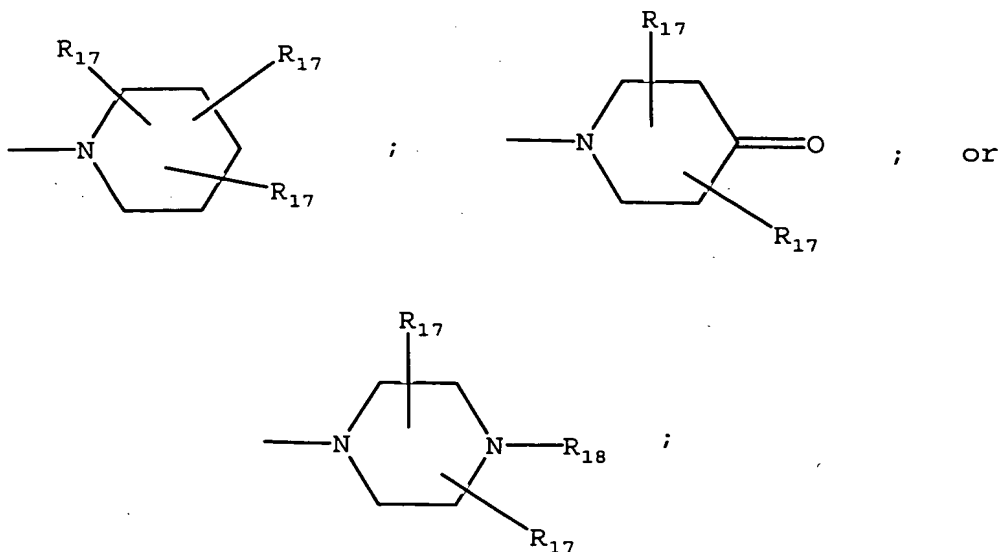
10

The invention provides a method of treating a subject suffering from anxiety which comprises administering to the subject an amount of compound effective to treat the  
 5 subject's anxiety wherein the compound has the structure:



wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

10 wherein X is;  $\text{NR}_{11}\text{R}_{12}$ ;



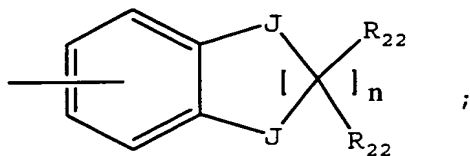
wherein  $\text{R}_{11}$  is H, straight chained or branched  $\text{C}_1\text{-C}_7$  alkyl,  $(\text{CH}_2)_q\text{-O-(CH}_2)_m\text{-CH}_3$ , aryl, or aryl  $(\text{C}_1\text{-C}_6)$  alkyl;

wherein  $R_{12}$  is straight chained or branched  $C_1$ - $C_7$  alkyl,  $(CH_2)_q-O-(CH_2)_m-CH_3$ , or  $-(CH_2)_m-Z$ ;

wherein  $R_{13}$  is a bicyclic alkyl ring system, adamantyl, noradamantyl,  $C_3$ - $C_{10}$  cycloalkyl, heteroaryl, aryl, aryl( $C_1$ - $C_6$ )alkyl,  $Q_1$  or  $Q_2$ ;

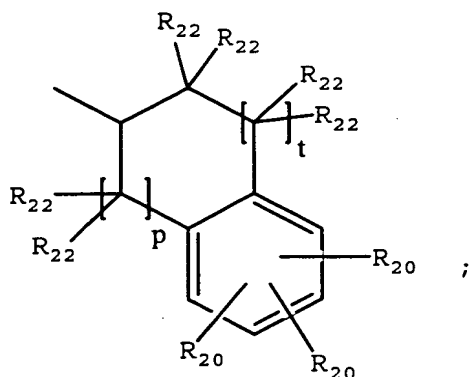
wherein aryl may be substituted with one or more  $C_1$ - $C_{10}$  straight chained or branched alkyl, aryl, heteroaryl, or  $N(R_{19})-Z$ ;

wherein  $Q_1$  is



15

wherein  $Q_2$  is

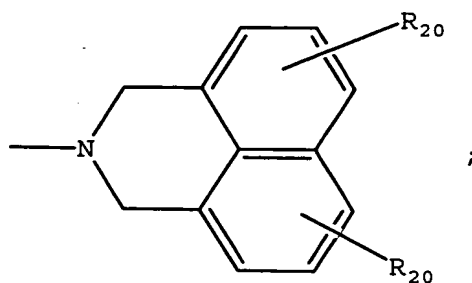
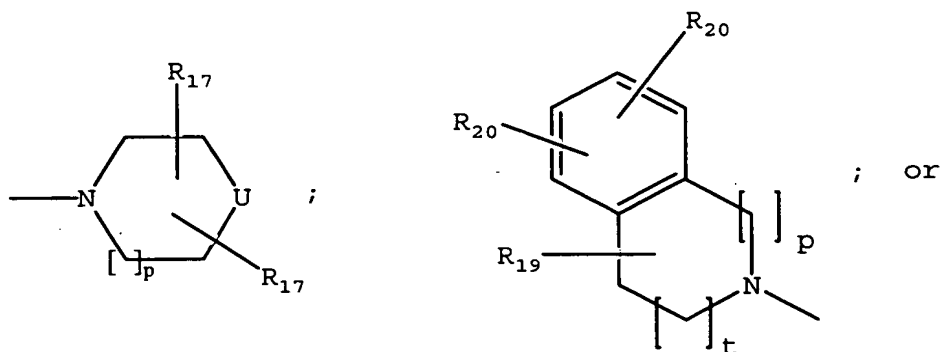


20 wherein each J is independently O, S,  $C(R_{22})_2$  or  $NR_4$ ;

wherein  $R_4$  is H; straight chained or branched  $C_1$ - $C_7$  alkyl,

monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$  cycloalkenyl or aryl;

5 wherein Y is  $NR_{14}R_{15}$ ;



10

wherein  $R_{14}$  is H, straight chained or branched  $C_1$ - $C_6$  alkyl,  $(CH_2)_q-O-(CH_2)_m-CH_3$ ,  $C_3$ - $C_6$  cycloalkyl, or  $(C(R_{19})_2)_m-Z$ ;

wherein  $R_{15}$  is straight chained or branched  $C_3$ - $C_6$  alkyl,  
 15  $(CH_2)_q-O-(CH_2)_m-CH_3$ ,  $C_3$ - $C_6$  cycloalkyl,  $(C(R_{19})_2)_mN(R_{16})_2$  or  
 $(C(R_{19})_2)_m-Z$ ;

wherein  $R_{16}$  is straight chained or branched  $C_1$ - $C_7$  alkyl,  
 straight chained or branched  $C_1$ - $C_7$  monofluoroalkyl,  
 20 straight chained or branched  $C_1$ - $C_7$  polyfluoroalkyl,



straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkynyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, -(CH<sub>2</sub>)<sub>m</sub>-Z, or (CH<sub>2</sub>)<sub>q</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-CH<sub>3</sub>;

5 wherein each R<sub>17</sub> is independently H; -OR<sub>21</sub>, -OCOR<sub>21</sub>, -COR<sub>21</sub>, -NCOR<sub>21</sub>, -N(R<sub>21</sub>)<sub>2</sub>, -CON(R<sub>21</sub>)<sub>2</sub>, -COOR<sub>21</sub>, straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> monofluoroalkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> polyfluoroalkyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkynyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, -(CH<sub>2</sub>)<sub>m</sub>-Z, or (CH<sub>2</sub>)<sub>n</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-CH<sub>3</sub>;

wherein R<sub>18</sub> is straight chained or branched C<sub>1</sub>-C<sub>6</sub> alkyl, -(CH<sub>2</sub>)<sub>m</sub>-Z, or (CH<sub>2</sub>)<sub>q</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-CH<sub>3</sub>;

15

wherein each R<sub>19</sub> is independently H, or straight chained or branched C<sub>1</sub>-C<sub>6</sub> alkyl;

wherein each R<sub>20</sub> is independently -H; straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl or alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl or C<sub>5</sub>-C<sub>7</sub> cycloalkenyl; -F, -Cl, -Br, or -I; -NO<sub>2</sub>; -N<sub>3</sub>; -CN; -OR<sub>21</sub>, -OCOR<sub>21</sub>, -COR<sub>21</sub>, -NCOR<sub>21</sub>, -N(R<sub>21</sub>)<sub>2</sub>, -CON(R<sub>21</sub>)<sub>2</sub>, or -COOR<sub>21</sub>; aryl or heteroaryl; or two R<sub>20</sub> groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each R<sub>21</sub> is independently -H; straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl or alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, aryl, or aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl;

wherein each  $R_{22}$  is independently H, F, Cl or  $C_1-C_4$  straight chained or branched alkyl;

5 wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

wherein p is an integer from 0 to 2 inclusive;

10

wherein q is an integer from 2 to 4 inclusive;

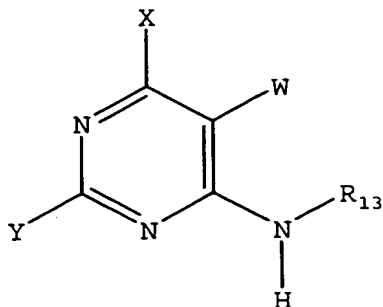
wherein t is 1 or 2;

15 wherein U is O,  $-NR_{16}$ , S,  $C(R_{17})_2$ , or  $-NSO_2R_{16}$ ;

wherein Z is  $C_3-C_{10}$  cycloalkyl,  $C_4-C_7$  cyclic ether,  $C_4-C_7$  cyclic thioether, aryl, or heteroaryl; or

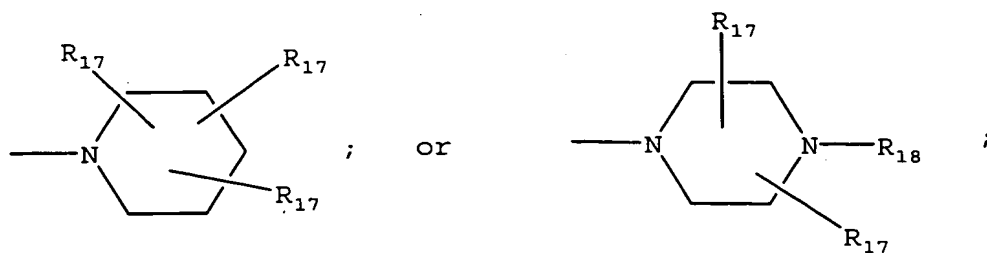
20 a pharmaceutically acceptable salt thereof.

The invention provides a method of treating a subject suffering from anxiety which comprises administering to  
25 the subject an amount of compound effective to treat the  
- subject's anxiety wherein the compound has the structure:



wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

5 wherein X is  $\text{NR}_{11}\text{R}_{12}$ ;



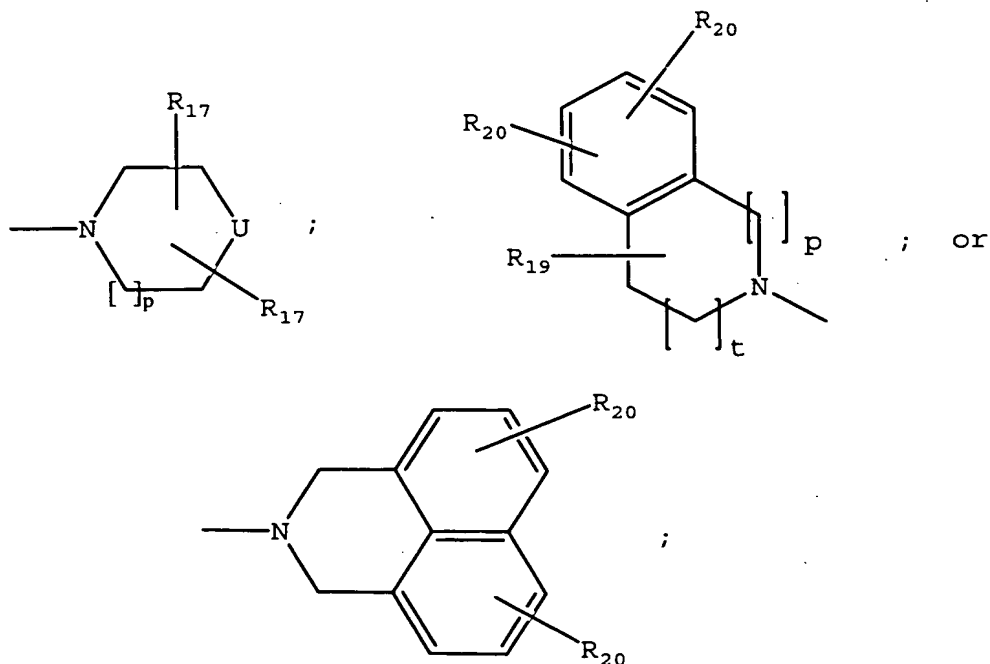
wherein  $\text{R}_{11}$  is H, straight chained or branched  $\text{C}_1\text{-C}_7$  alkyl,  $(\text{CH}_2)_q\text{-O-}(\text{CH}_2)_m\text{-CH}_3$ , aryl or aryl( $\text{C}_1\text{-C}_6$ )alkyl;

10 wherein  $\text{R}_{12}$  is straight chained or branched  $\text{C}_1\text{-C}_7$  alkyl,  $(\text{CH}_2)_q\text{-O-}(\text{CH}_2)_m\text{-CH}_3$ , or  $-(\text{CH}_2)_m\text{-Z}$ ;

wherein  $\text{R}_{13}$  is a bicyclic alkyl ring system, aryl or aryl( $\text{C}_1\text{-C}_6$ )alkyl;

15

wherein Y is  $\text{NR}_{14}\text{R}_{15}$ ;



wherein  $R_{14}$  is H, straight chained or branched  $C_1$ - $C_6$  alkyl,  $(CH_2)_q-O-(CH_2)_m-CH_3$ ,  $C_3$ - $C_6$  cycloalkyl, or  $(C(R_{19})_2)_m-Z$ ;

5

wherein  $R_{15}$  is straight chained or branched  $C_3$ - $C_6$  alkyl,  $(CH_2)_q-O-(CH_2)_m-CH_3$ ,  $C_3$ - $C_6$  cycloalkyl, or  $(C(R_{19})_2)_m-Z$ ;

wherein U is O,  $-NR_{16}$ , S,  $C(R_{17})_2$ , or  $-NSO_2R_{16}$ ;

10

wherein Z is  $C_3$ - $C_{10}$  cycloalkyl, aryl, or heteroaryl;

wherein  $R_{16}$  is straight chained or branched  $C_1$ - $C_7$  alkyl, straight chained or branched  $C_1$ - $C_7$  monofluoroalkyl, straight chained or branched  $C_1$ - $C_7$  polyfluoroalkyl, straight chained or branched  $C_2$ - $C_7$  alkenyl, straight chained or branched  $C_2$ - $C_7$  alkynyl,  $C_5$ - $C_7$  cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_q-O-(CH_2)_m-CH_3$ ;

15

wherein each  $R_{17}$  is independently H;  $-OR_{21}$ ,  $-OCOR_{21}$ ,  $-COR_{21}$ ,  $-NCOR_{21}$ ,  $-N(R_{21})_2$ ,  $-CON(R_{21})_2$ ,  $-COOR_{21}$ , straight chained or branched  $C_1$ - $C_7$  alkyl, straight chained or branched  $C_1$ - $C_7$  monofluoroalkyl, straight chained or branched  $C_1$ - $C_7$  polyfluoroalkyl, straight chained or branched  $C_2$ - $C_7$  alkenyl, straight chained or branched  $C_2$ - $C_7$  alkynyl,  $C_5$ - $C_7$  cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_n-O-(CH_2)_m-CH_3$ ;

wherein  $R_{18}$  is straight chained or branched  $C_1$ - $C_6$  alkyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_q-O-(CH_2)_m-CH_3$ ;

wherein each  $R_{19}$  is independently H, or straight chained or branched  $C_1$ - $C_6$  alkyl;

wherein each  $R_{20}$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl or  $C_5$ - $C_7$  cycloalkenyl; -F, -Cl, -Br, or -I;  $-NO_2$ ;  $-N_3$ ; -CN;  $-OR_{21}$ ,  $-OCOR_{21}$ ,  $-COR_{21}$ ,  $-NCOR_{21}$ ,  $-N(R_{21})_2$ ,  $-CON(R_{21})_2$ , or  $-COOR_{21}$ ; aryl or heteroaryl; or two  $R_{20}$  groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each  $R_{21}$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$  cycloalkenyl, aryl or aryl( $C_1$ - $C_6$ )alkyl;

wherein each  $m$  is an integer from 0 to 4 inclusive;

wherein each  $n$  is an integer from 1 to 4 inclusive;

wherein p is an integer from 0 to 2 inclusive;

wherein q is an integer from 2 to 4 inclusive;

5

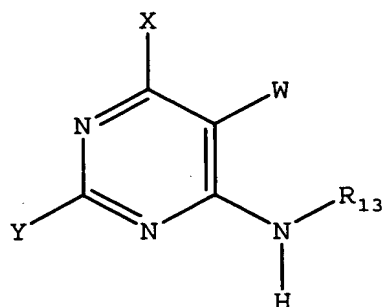
wherein t is 1 or 2; or

a pharmaceutically acceptable salt thereof.

10

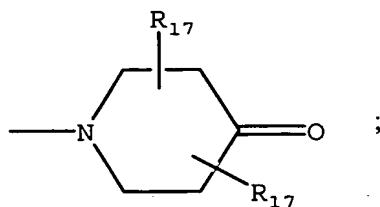
The invention provides a method of treating a subject suffering from anxiety which comprises administering to the subject an amount of compound effective to treat the subject's anxiety wherein the compound has the structure:

15



wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

20 wherein X is N(CH<sub>3</sub>)<sub>2</sub> or

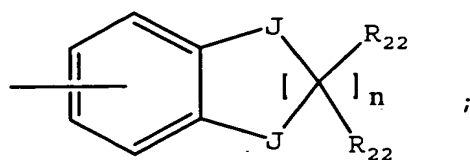


wherein  $R_{13}$  is an aryl, adamantyl, noradamantyl,  $C_3$ - $C_{10}$  cycloalkyl, heteroaryl,  $Q_1$  or  $Q_2$ ;

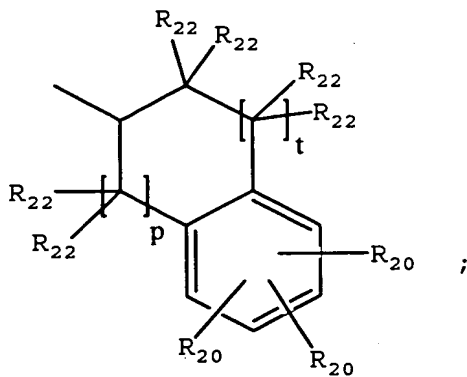
- 5 wherein aryl may be substituted with one or more  $C_1$ - $C_{10}$  straight chained or branched alkyl, aryl, heteroaryl, or  $N(R_{19})-Z$ ;

wherein  $Q_1$  is

10



wherein  $Q_2$  is

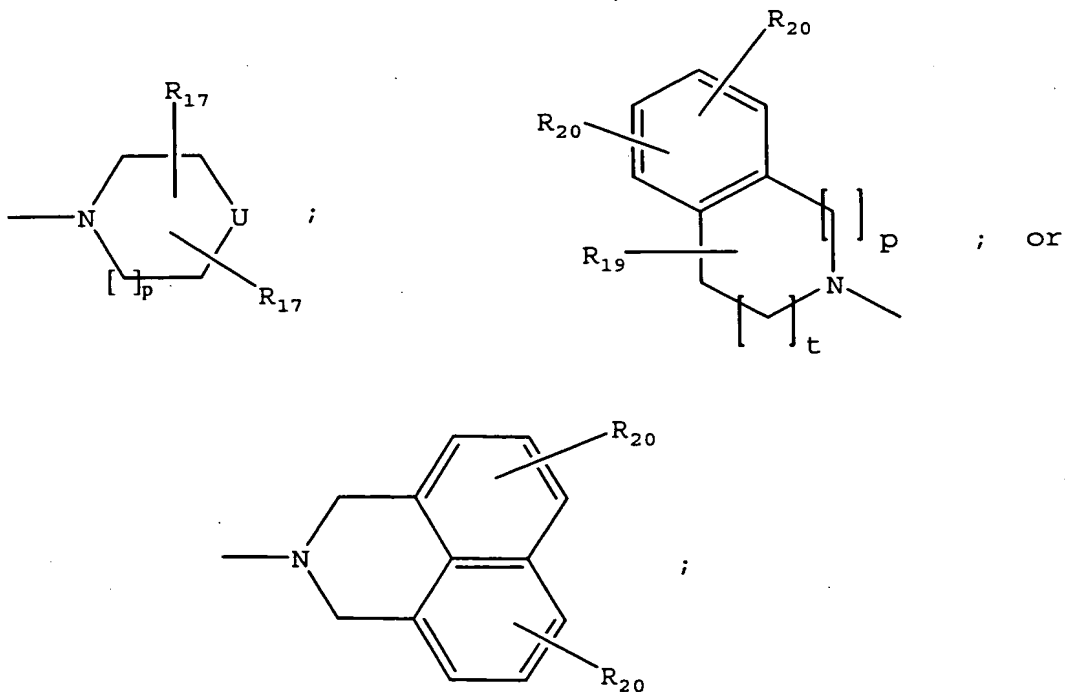


15

wherein each  $J$  is independently  $O$ ,  $S$ ,  $C(R_{22})_2$  or  $NR_4$ ;

- wherein  $R_4$  is  $-H$ ; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight  
 20 chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$  cycloalkenyl or aryl;

wherein Y is  $\text{NR}_{14}\text{R}_{15}$ ;



5

wherein  $\text{R}_{14}$  is H, straight chained or branched  $\text{C}_1\text{-C}_6$  alkyl,  $(\text{CH}_2)_q\text{-O-(CH}_2)_m\text{-CH}_3$ ,  $\text{C}_3\text{-C}_6$  cycloalkyl, or  $(\text{C}(\text{R}_{19})_2)_m\text{-Z}$ ;

wherein  $\text{R}_{15}$  is straight chained or branched  $\text{C}_3\text{-C}_6$  alkyl,  
 10  $(\text{CH}_2)_q\text{-O-(CH}_2)_m\text{-CH}_3$ ,  $\text{C}_3\text{-C}_6$  cycloalkyl, or  $(\text{C}(\text{R}_{19})_2)_m\text{-Z}$ ;

wherein U is O,  $\text{-NR}_{16}$ , S,  $\text{C}(\text{R}_{17})_2$ , or  $\text{-NSO}_2\text{R}_{16}$ ;

wherein Z is  $\text{C}_3\text{-C}_{10}$  cycloalkyl, aryl, or heteroaryl;

15

wherein  $\text{R}_{16}$  is straight chained or branched  $\text{C}_1\text{-C}_7$  alkyl,  
 straight chained or branched  $\text{C}_1\text{-C}_7$  monofluoroalkyl,  
 straight chained or branched  $\text{C}_1\text{-C}_7$  polyfluoroalkyl,



straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkynyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, - (CH<sub>2</sub>)<sub>m</sub>-Z, or (CH<sub>2</sub>)<sub>q</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-CH<sub>3</sub>;

- 5 wherein each R<sub>17</sub> is independently H; -OR<sub>21</sub>, -OCOR<sub>21</sub>, -COR<sub>21</sub>, -NCOR<sub>21</sub>, -N(R<sub>21</sub>)<sub>2</sub>, -CON(R<sub>21</sub>)<sub>2</sub>, -COOR<sub>21</sub>, straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> monofluoroalkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> polyfluoroalkyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkynyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, - (CH<sub>2</sub>)<sub>m</sub>-Z, or (CH<sub>2</sub>)<sub>n</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-CH<sub>3</sub>;

wherein R<sub>18</sub> is straight chained or branched C<sub>1</sub>-C<sub>6</sub> alkyl, - (CH<sub>2</sub>)<sub>m</sub>-Z, or (CH<sub>2</sub>)<sub>q</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-CH<sub>3</sub>;

- 15 wherein each R<sub>19</sub> is independently H, or straight chained or branched C<sub>1</sub>-C<sub>6</sub> alkyl;

- wherein each R<sub>20</sub> is independently -H; straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl or alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl or C<sub>5</sub>-C<sub>7</sub> cycloalkenyl; -F, -Cl, -Br, or -I; -NO<sub>2</sub>; -N<sub>3</sub>; -CN; -OR<sub>21</sub>, -OCOR<sub>21</sub>, -COR<sub>21</sub>, -NCOR<sub>21</sub>, -N(R<sub>21</sub>)<sub>2</sub>, -CON(R<sub>21</sub>)<sub>2</sub>, or -COOR<sub>21</sub>; aryl or heteroaryl; or two R<sub>20</sub> groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

- wherein each R<sub>21</sub> is independently -H; straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl or alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, aryl or aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl;

wherein each  $R_{22}$  is independently H, F, Cl or  $C_1-C_4$  straight chained or branched alkyl;

wherein each m is an integer from 0 to 4 inclusive;

5

wherein each n is an integer from 1 to 4 inclusive;

wherein p is an integer from 0 to 2 inclusive;

10 wherein q is an integer from 2 to 4 inclusive;

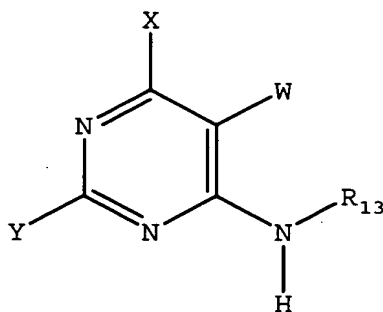
wherein t is 1 or 2; or

a pharmaceutically acceptable salt thereof.

15

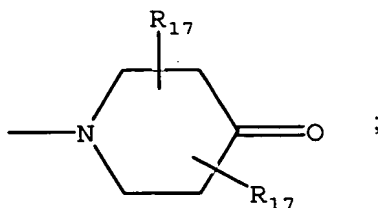
The invention provides a method of treating a subject suffering from anxiety which comprises administering to the subject an amount of compound effective to treat the subject's anxiety wherein the compound has the structure:

20



wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

25 wherein X is  $N(CH_3)_2$  or



wherein  $R_{13}$  is a bicyclic alkyl ring system, aryl or aryl( $C_1$ - $C_6$ )alkyl;

5

wherein Y is  $NR_{14}R_{15}$ ;

wherein  $R_{14}$  is H, straight chained or branched  $C_1$ - $C_6$  alkyl,  $(CH_2)_q-O-(CH_2)_m-CH_3$ ,  $C_3$ - $C_6$  cycloalkyl, or  $(C(R_{19})_2)_m-Z$ ;

10

wherein  $R_{15}$  is  $(C(R_{19})_2)_m-N(R_{16})_2$ ;

wherein Z is  $C_3$ - $C_{10}$  cycloalkyl, aryl, or heteroaryl;

15 wherein  $R_{16}$  is straight chained or branched  $C_1$ - $C_7$  alkyl, straight chained or branched  $C_1$ - $C_7$  monofluoroalkyl, straight chained or branched  $C_1$ - $C_7$  polyfluoroalkyl, straight chained or branched  $C_2$ - $C_7$  alkenyl, straight chained or branched  $C_2$ - $C_7$  alkynyl,  $C_5$ - $C_7$  cycloalkenyl, -  
20  $(CH_2)_m-Z$ , or  $(CH_2)_q-O-(CH_2)_m-CH_3$ ;

wherein each  $R_{17}$  is independently H;  $-OR_{21}$ ,  $-OCOR_{21}$ ,  $-COR_{21}$ ,  $-NCOR_{21}$ ,  $-N(R_{21})_2$ ,  $-CON(R_{21})_2$ ,  $-COOR_{21}$ , straight chained or branched  $C_1$ - $C_7$  alkyl, straight chained or branched  $C_1$ - $C_7$   
25 monofluoroalkyl, straight chained or branched  $C_1$ - $C_7$  polyfluoroalkyl, straight chained or branched  $C_2$ - $C_7$  alkenyl, straight chained or branched  $C_2$ - $C_7$  alkynyl,  $C_5$ - $C_7$  cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_n-O-(CH_2)_m-CH_3$ ;

wherein each  $R_{19}$  is independently H, or straight chained or branched  $C_1-C_6$  alkyl;

wherein each  $R_{21}$  is independently -H; straight chained or  
 5 branched  $C_1-C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2-C_7$  alkenyl or alkynyl;  $C_3-C_7$  cycloalkyl,  $C_5-C_7$  cycloalkenyl, aryl or aryl( $C_1-C_6$ )alkyl;

10 wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

wherein q is an integer from 2 to 4 inclusive; or

15

a pharmaceutically acceptable salt thereof.

As used in the present invention, the term "bicyclic alkyl ring systems" includes, but is not limited to,  
 20 bicyclo[2.2.1]heptane, bicyclo[3.1.1]heptane and bicyclo[2.2.2]octane. In addition, the bicyclic alkyl ring systems may be substituted with one or more of the following: -F, -NO<sub>2</sub>, -CN, straight chained or branched  $C_1-C_7$  alkyl, straight chained or branched  $C_1-C_7$   
 25 monofluoroalkyl, straight chained or branched  $C_1-C_7$  polyfluoroalkyl, straight chained or branched  $C_2-C_7$  alkenyl, straight chained or branched  $C_2-C_7$  alkynyl,  $C_3-C_7$  cycloalkyl,  $C_5-C_7$  cycloalkenyl, -N( $R_{21}$ )<sub>2</sub>, -OR<sub>21</sub>, -COR<sub>21</sub>, -CO<sub>2</sub>R<sub>21</sub>, -CON( $R_{21}$ )<sub>2</sub> or (CH<sub>2</sub>)<sub>n</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-CH<sub>3</sub>.

30

As used in the present invention, the term "cycloalkyl" includes,  $C_3-C_7$  cycloalkyl moieties which may be

substituted with one or more of the following: -F, -NO<sub>2</sub>,  
 -CN, straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, straight  
 chained or branched C<sub>1</sub>-C<sub>7</sub> monofluoroalkyl, straight  
 chained or branched C<sub>1</sub>-C<sub>7</sub> polyfluoroalkyl, straight  
 5 chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl, straight chained or  
 branched C<sub>2</sub>-C<sub>7</sub> alkynyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>3</sub>-C<sub>7</sub>  
 monofluorocycloalkyl, C<sub>3</sub>-C<sub>7</sub> polyfluorocycloalkyl, C<sub>5</sub>-C<sub>7</sub>  
 cycloalkenyl, -N(R<sub>4</sub>)<sub>2</sub>, -OR<sub>4</sub>, -COR<sub>4</sub>, -NCOR<sub>4</sub>, -CO<sub>2</sub>R<sub>4</sub>, -  
 CON(R<sub>4</sub>)<sub>2</sub> or (CH<sub>2</sub>)<sub>n</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-CH<sub>3</sub>.

10

As used in the present invention, the term "cyclohexyl"  
 includes, cyclohexyl groups which may be substituted with  
 one or more of the following: -F, -NO<sub>2</sub>, -CN, straight  
 chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, straight chained or  
 15 branched C<sub>1</sub>-C<sub>7</sub> monofluoroalkyl, straight chained or  
 branched C<sub>1</sub>-C<sub>7</sub> polyfluoroalkyl, straight chained or  
 branched C<sub>2</sub>-C<sub>7</sub> alkenyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub>  
 alkynyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>3</sub>-C<sub>7</sub> monofluorocycloalkyl, C<sub>3</sub>-C<sub>7</sub>  
 polyfluorocycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, -N(R<sub>4</sub>)<sub>2</sub>, -OR<sub>4</sub>, -  
 20 COR<sub>4</sub>, -NCOR<sub>4</sub>, -CO<sub>2</sub>R<sub>4</sub>, -CON(R<sub>4</sub>)<sub>2</sub> or (CH<sub>2</sub>)<sub>n</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-CH<sub>3</sub>.

As used in the present invention, the term "cycloalkenyl"  
 includes, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl moieties which may be  
 substituted with one or more of the following: -F, -Cl,  
 25 -Br, -I, -NO<sub>2</sub>, -CN, straight chained or branched C<sub>1</sub>-C<sub>7</sub>  
 alkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> monofluoroalkyl,  
 straight chained or branched C<sub>1</sub>-C<sub>7</sub> polyfluoroalkyl,  
 straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl, straight  
 chained or branched C<sub>2</sub>-C<sub>7</sub> alkynyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>3</sub>-C<sub>7</sub>  
 30 monofluorocycloalkyl, C<sub>3</sub>-C<sub>7</sub> polyfluorocycloalkyl, C<sub>5</sub>-C<sub>7</sub>  
 cycloalkenyl, -N(R<sub>4</sub>)<sub>2</sub>, -OR<sub>4</sub>, -COR<sub>4</sub>, -NCOR<sub>4</sub>, -CO<sub>2</sub>R<sub>4</sub>, -  
 CON(R<sub>4</sub>)<sub>2</sub> or (CH<sub>2</sub>)<sub>n</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-CH<sub>3</sub>.

In the present invention, the term "heteroaryl" is used to include five and six membered unsaturated rings that may contain one or more oxygen, sulfur, or nitrogen atoms. Examples of heteroaryl groups include, but are not limited to, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, and triazinyl.

In addition the term "heteroaryl" is used to include fused bicyclic ring systems that may contain one or more heteroatoms such as oxygen, sulfur and nitrogen. Examples of such heteroaryl groups include, but are not limited to, indoliziny, indolyl, isoindolyl, benzo[b]furanyl, benzo[b]thiophenyl, indazolyl, benzimidazolyl, purinyl, benzoxazolyl, benzisoxazolyl, benzo[b]thiazolyl, imidazo[2,1-b]thiazolyl, cinnolinyl, quinazolinyl, quinoxalinyl, 1,8-naphthyridinyl, pteridinyl, quinolinyl, isoquinolinyl, phthalimidyl and 2,1,3-benzothiazolyl.

The term "heteroaryl" also includes those chemical moieties recited above which may be substituted with one or more of the following: -F, -Cl, -Br, -I, -NO<sub>2</sub>, -CN, straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> monofluoroalkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> polyfluoroalkyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkynyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>3</sub>-C<sub>7</sub> monofluorocycloalkyl, C<sub>3</sub>-C<sub>7</sub> polyfluorocycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, -N(R<sub>4</sub>)<sub>2</sub>, -OR<sub>4</sub>, -COR<sub>4</sub>, -NCOR<sub>4</sub>, -CO<sub>2</sub>R<sub>4</sub>, -CON(R<sub>4</sub>)<sub>2</sub> or (CH<sub>2</sub>)<sub>n</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-CH<sub>3</sub>.

The term "heteroaryl" further includes the N-oxides of those chemical moieties recited above which include at least one nitrogen atom.

5

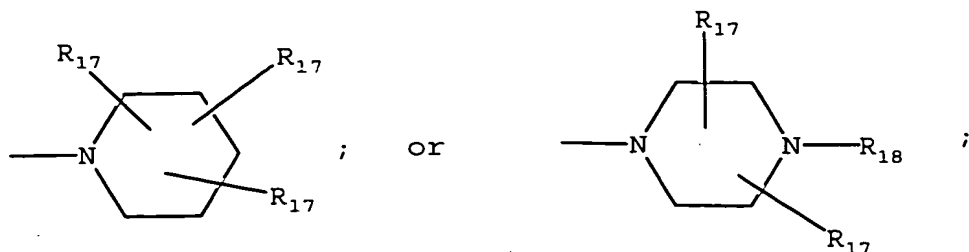
In the present invention the term "aryl" is phenyl or naphthyl. The term "aryl" also includes phenyl and naphthyl which may be substituted with one or more of the following: -F, -Cl, -Br, -I, -NO<sub>2</sub>, -CN, straight chained  
 10 or branched C<sub>1</sub>-C<sub>7</sub> alkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> monofluoroalkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> polyfluoroalkyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkynyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>3</sub>-C<sub>7</sub> monofluorocycloalkyl, C<sub>3</sub>-C<sub>7</sub>  
 15 polyfluorocycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, -N(R<sub>4</sub>)<sub>2</sub>, -OR<sub>4</sub>, -SR<sub>4</sub>, -OCOR<sub>4</sub>, -COR<sub>4</sub>, -NCOR<sub>4</sub>, -CO<sub>2</sub>R<sub>4</sub>, -CON(R<sub>4</sub>)<sub>2</sub> or (CH<sub>2</sub>)<sub>n</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-CH<sub>3</sub>.

20 In one embodiment of any of the methods described herein, the compound is enantiomerically and diasteriomERICALLY pure. In one embodiment, the compound is enantiomerically or diasteriomERICALLY pure.

25 In one embodiment, the compound can be administered orally.

In one embodiment, X is:

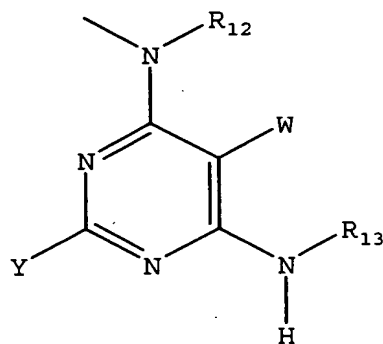
30



In one embodiment, X is  $\text{NR}_{11}\text{R}_{12}$  and  $\text{R}_{11}$  is H or straight chained or branched  $\text{C}_1\text{-C}_7$  alkyl.

5

In one embodiment, the compound has the structure:



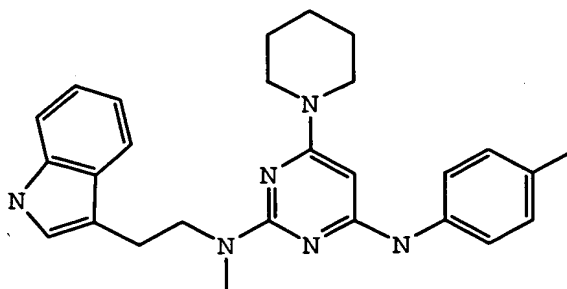
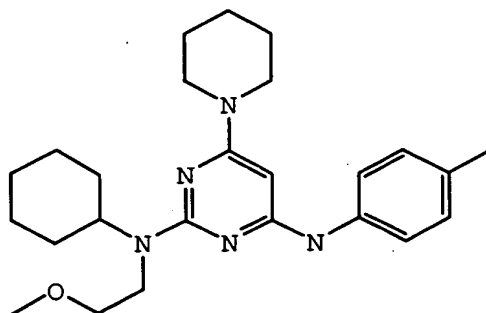
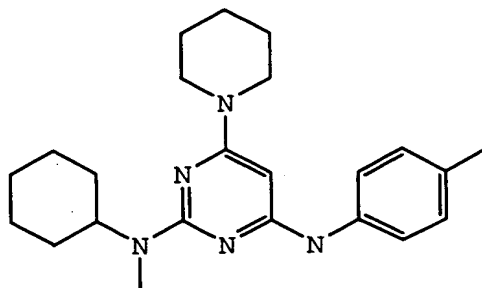
In one embodiment,  $\text{R}_{13}$  is a bicyclic alkyl ring system,  
10 cyclohexyl or aryl.

In one embodiment,  $\text{R}_{14}$  is H, straight chained or branched  $\text{C}_1\text{-C}_6$  alkyl or  $(\text{CH}_2)_q\text{-O-(CH}_2)_m\text{-CH}_3$ .

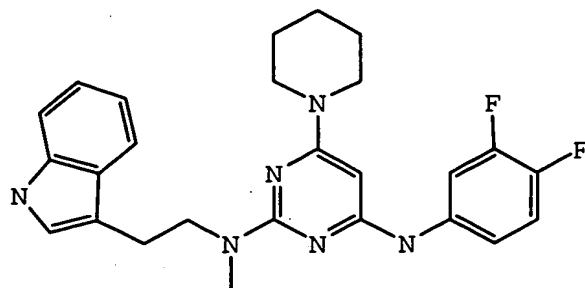
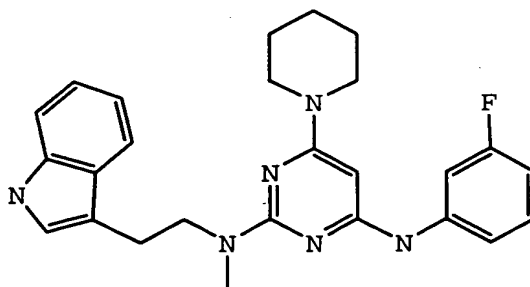
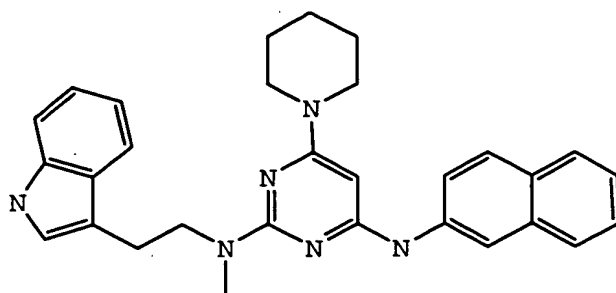
15



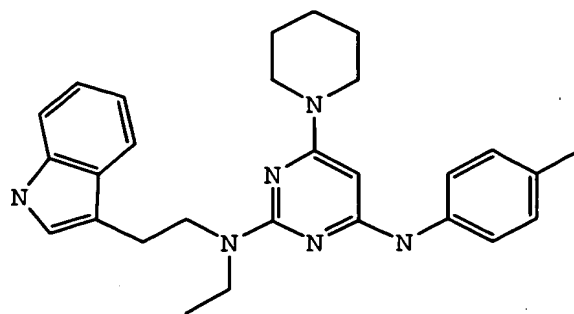
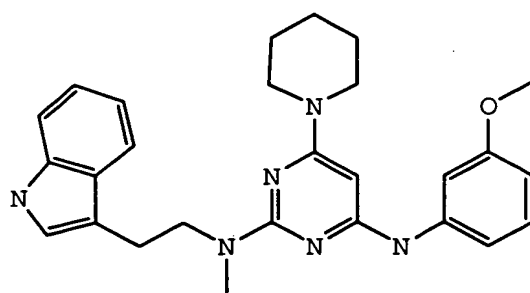
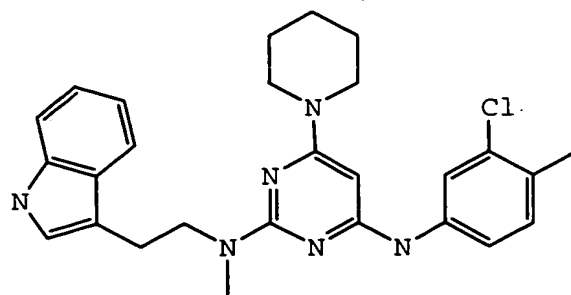
In one embodiment, the compound is selected from the group consisting of:

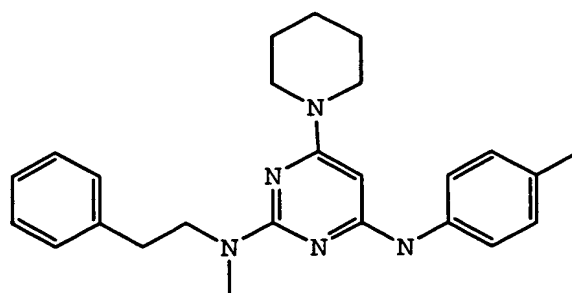
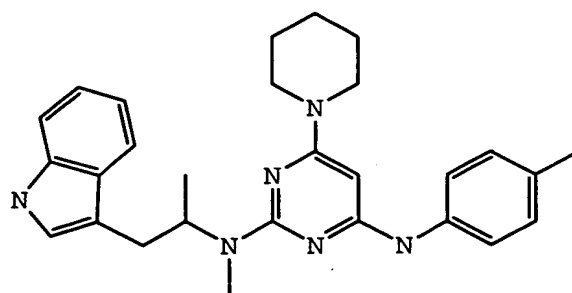
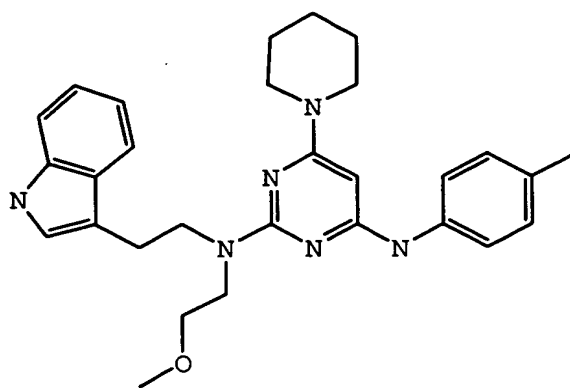


183



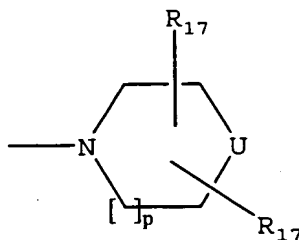
184





5

In one embodiment, Y is

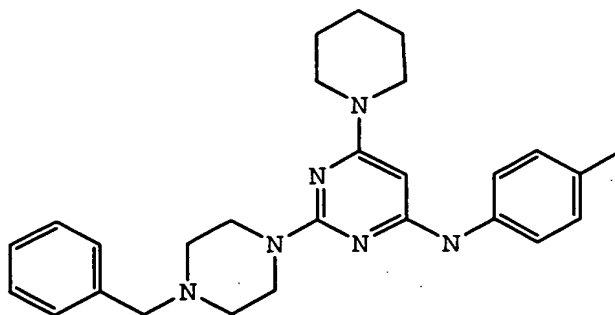


In one embodiment, U is  $\text{NR}_{16}$ .

5 In one embodiment,  $\text{R}_{16}$  is  $(\text{CH}_2)_m\text{-Z}$ .

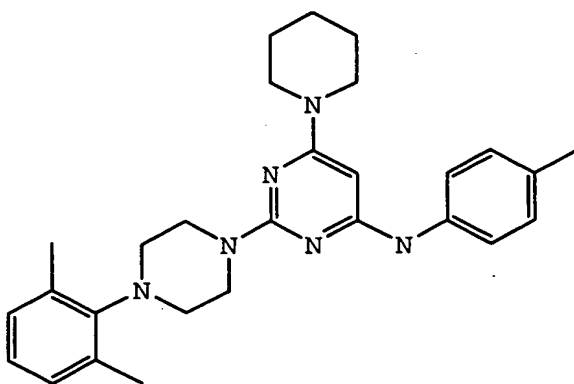
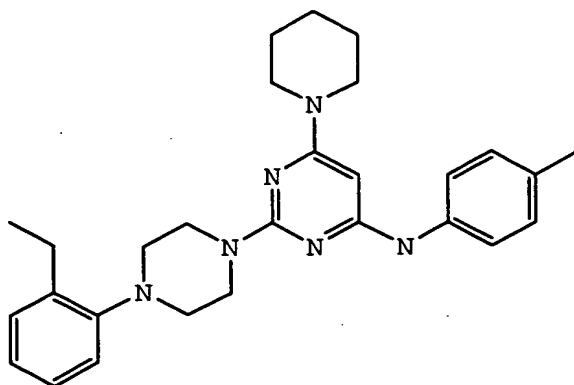
In one embodiment, Z is aryl or heteroaryl.

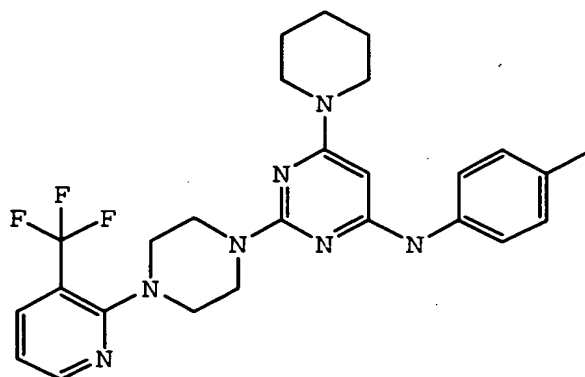
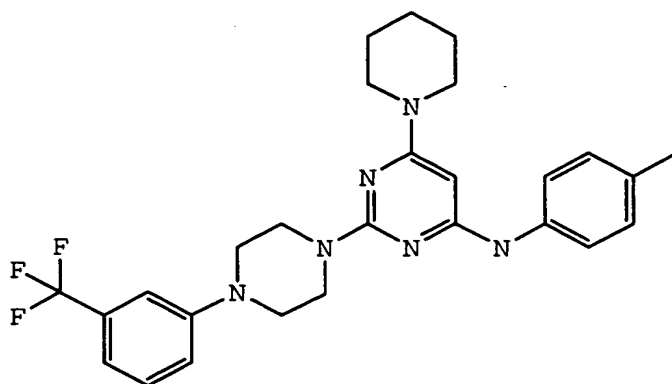
In one embodiment, the compound is selected from the  
 10 group consisting of:



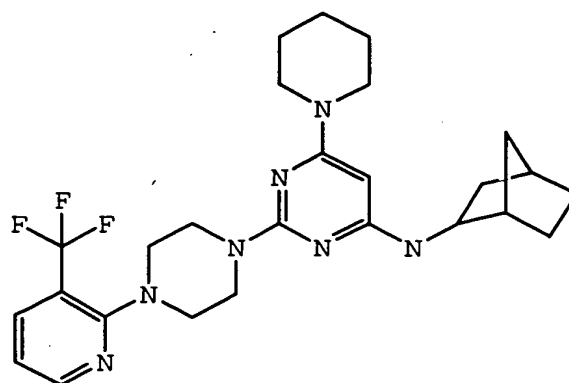
15

187

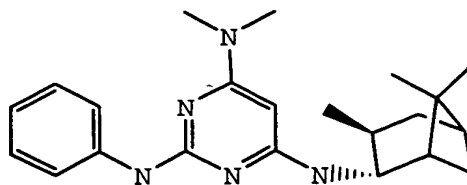
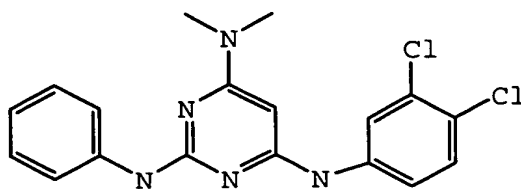
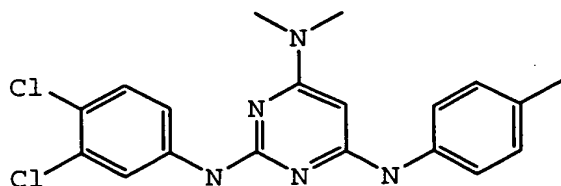




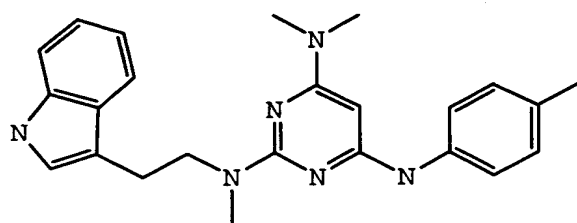
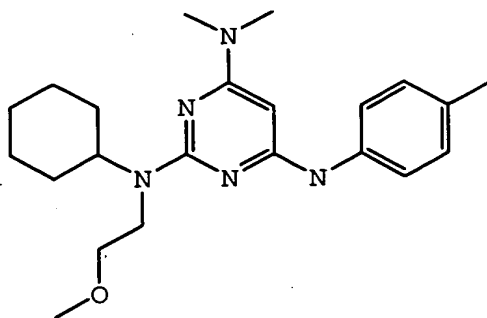
; and



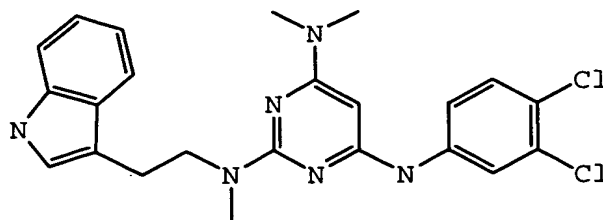
In one embodiment, the compound is selected from the group consisting of:



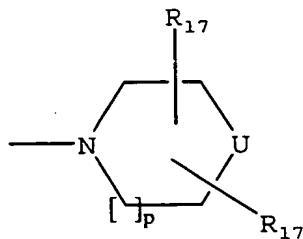




; and



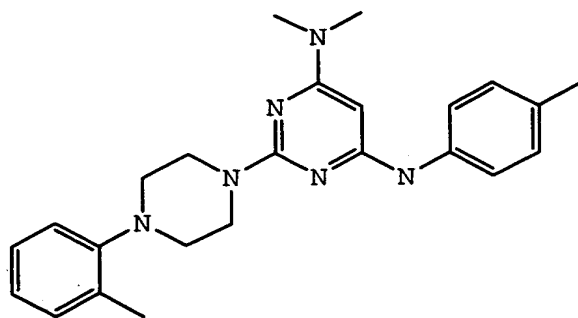
In one embodiment, Y is



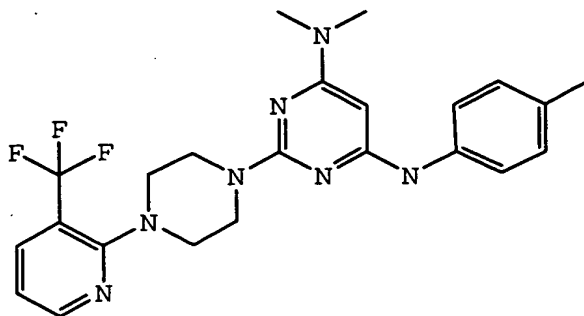
In one embodiment, U is  $\text{NR}_{16}$ .

5

In one embodiment, the compound is

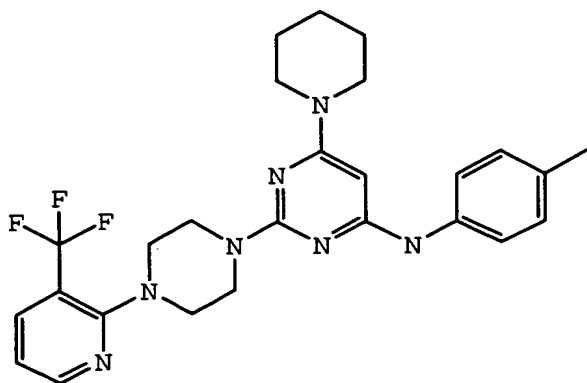


; or



10

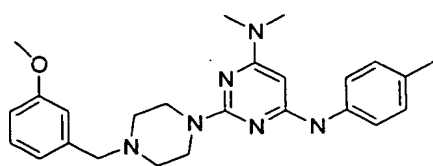
In one embodiment, the compound is



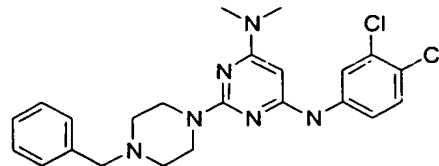
5

In one embodiment, the compound is selected from the group consisting of:

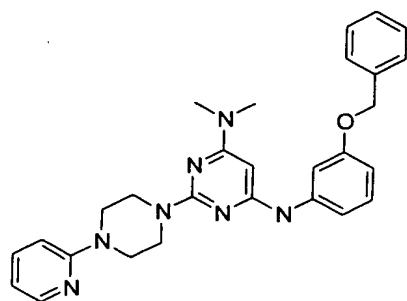
10



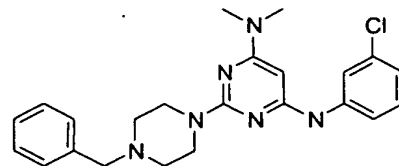
;



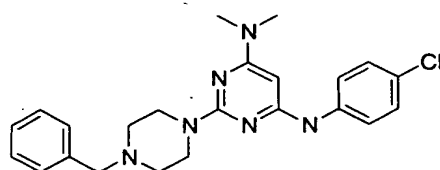
;



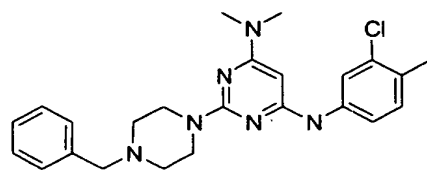
;



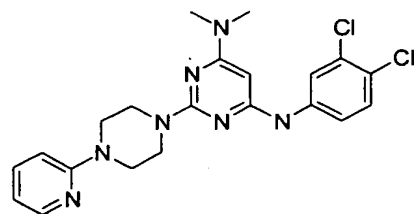
;



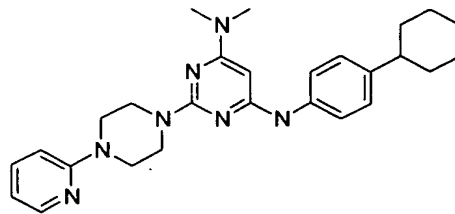
;



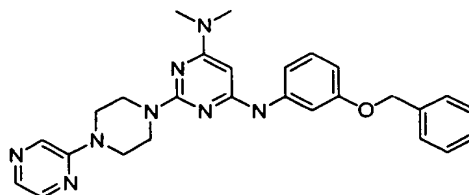
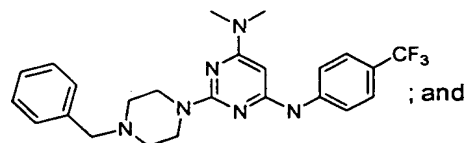
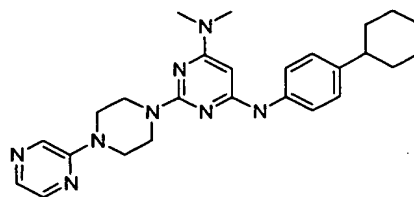
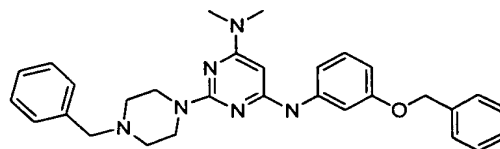
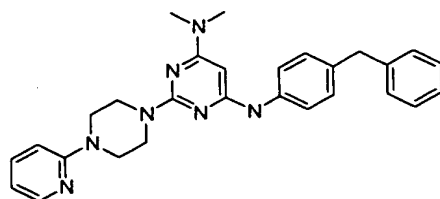
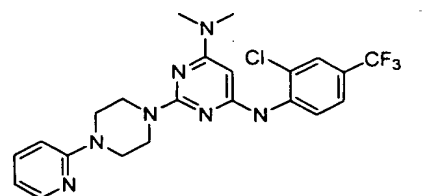
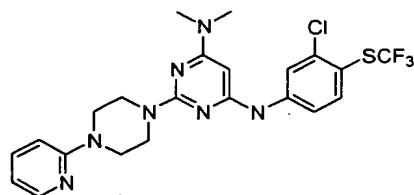
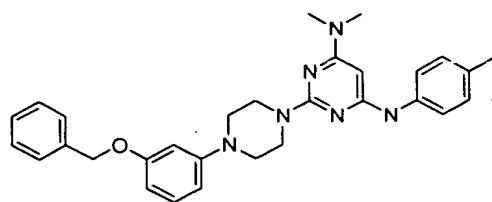
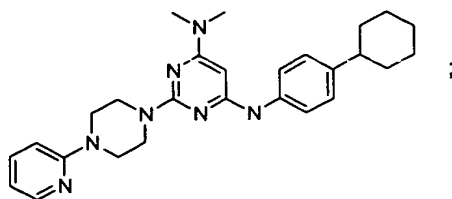
;



; and



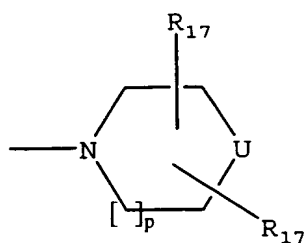
- 5 In one embodiment, the compound is selected from the group consisting of:



In one embodiment, X is  $\text{N}(\text{CH}_3)_2$ .

5

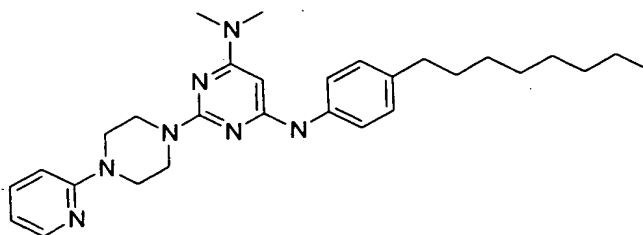
In one embodiment, Y is



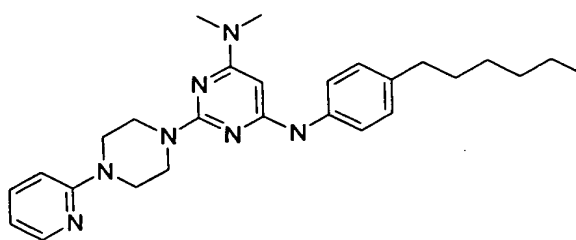
In one embodiment,  $R_{13}$  is an aryl substituted with a  $C_1$ - $C_{10}$  straight chained alkyl.

5

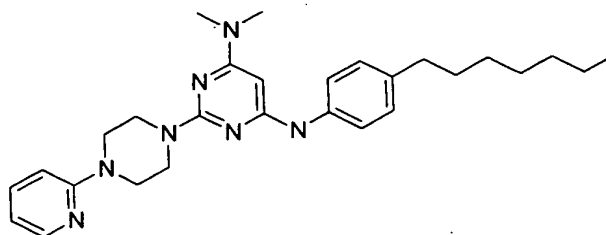
In one embodiment, the compound is selected from a group consisting of:



;

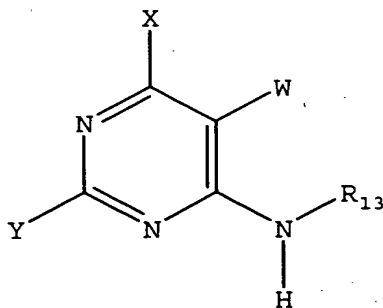


; and



10

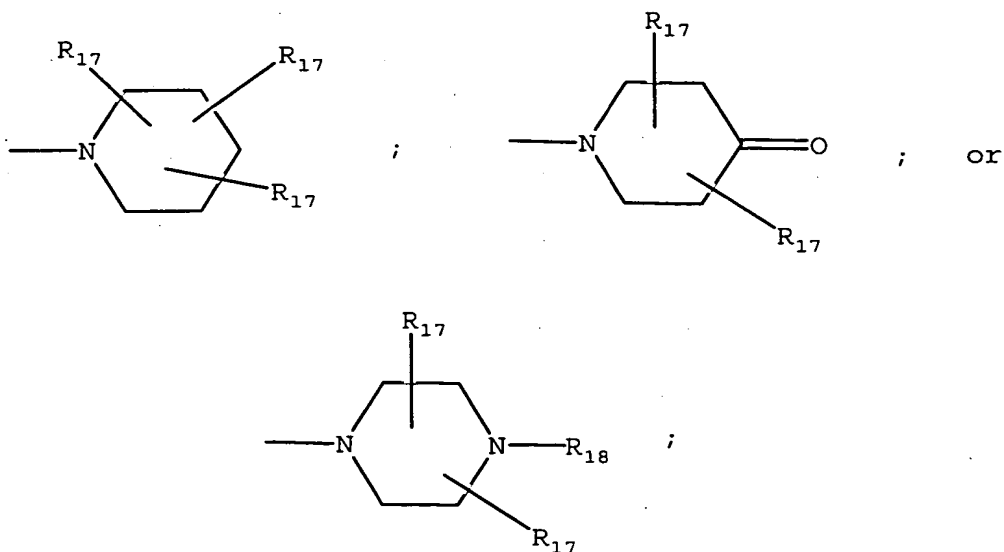
The invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound having the structure:



5

wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

wherein X is;  $\text{NR}_{11}\text{R}_{12}$ ;



10

wherein  $\text{R}_{11}$  is H, straight chained or branched  $\text{C}_1\text{-C}_7$  alkyl,  $(\text{CH}_2)_q\text{-O-(CH}_2)_m\text{-CH}_3$ , aryl, or aryl  $(\text{C}_1\text{-C}_6)$  alkyl;

wherein  $\text{R}_{12}$  is straight chained or branched  $\text{C}_1\text{-C}_7$  alkyl,

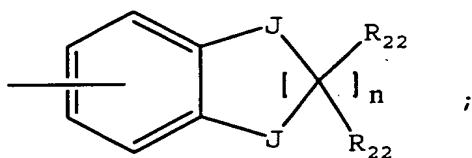
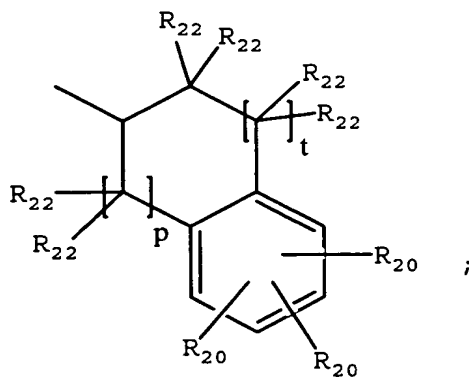
$(\text{CH}_2)_q\text{-O-}(\text{CH}_2)_m\text{-CH}_3$ , or  $\text{-(CH}_2)_m\text{-Z}$ ;

wherein  $\text{R}_{13}$  is a bicyclic alkyl ring system, adamantyl, noradamantyl,  $\text{C}_3\text{-C}_{10}$  cycloalkyl, heteroaryl, aryl, aryl( $\text{C}_1\text{-C}_6$ )alkyl,  $\text{Q}_1$  or  $\text{Q}_2$ ;

wherein aryl may be substituted with one or more  $\text{C}_1\text{-C}_{10}$  straight chained or branched alkyl, aryl, heteroaryl, or  $\text{N(R}_{19})\text{-Z}$ ;

10

wherein  $\text{Q}_1$  is

15 wherein  $\text{Q}_2$  is

wherein each  $\text{J}$  is independently  $\text{O}$ ,  $\text{S}$ ,  $\text{C(R}_{22})_2$  or  $\text{NR}_4$ ;

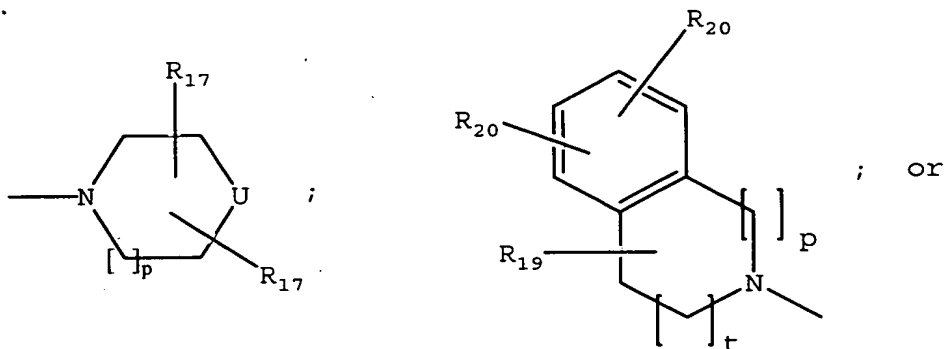
20

wherein  $\text{R}_4$  is  $\text{H}$ ; straight chained or branched  $\text{C}_1\text{-C}_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or

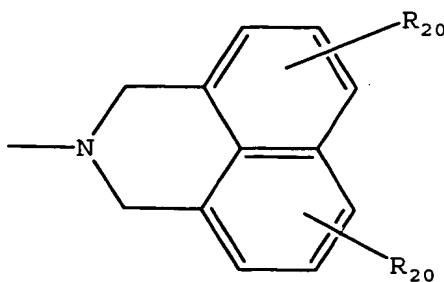


branched C<sub>2</sub>-C<sub>7</sub> alkenyl or alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl or aryl;

wherein Y is NR<sub>14</sub>R<sub>15</sub>;



5



10 wherein R<sub>14</sub> is H, straight chained or branched C<sub>1</sub>-C<sub>6</sub> alkyl, (CH<sub>2</sub>)<sub>q</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-CH<sub>3</sub>, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, or (C(R<sub>19</sub>)<sub>2</sub>)<sub>m</sub>-Z;

wherein R<sub>15</sub> is straight chained or branched C<sub>3</sub>-C<sub>6</sub> alkyl, (CH<sub>2</sub>)<sub>q</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-CH<sub>3</sub>, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, (C(R<sub>19</sub>)<sub>2</sub>)<sub>m</sub>N(R<sub>16</sub>)<sub>2</sub> or  
 15 (C(R<sub>19</sub>)<sub>2</sub>)<sub>m</sub>-Z;

wherein R<sub>16</sub> is straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> monofluoroalkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> polyfluoroalkyl,  
 20 straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl, straight

chained or branched C<sub>2</sub>-C<sub>7</sub> alkynyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, -  
(CH<sub>2</sub>)<sub>m</sub>-Z, or (CH<sub>2</sub>)<sub>q</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-CH<sub>3</sub>;

wherein each R<sub>17</sub> is independently H; -OR<sub>21</sub>, -OCOR<sub>21</sub>, -COR<sub>21</sub>,  
5 -NCOR<sub>21</sub>, -N(R<sub>21</sub>)<sub>2</sub>, -CON(R<sub>21</sub>)<sub>2</sub>, -COOR<sub>21</sub>, straight chained or  
branched C<sub>1</sub>-C<sub>7</sub> alkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub>  
monofluoroalkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub>  
polyfluoroalkyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub>  
alkenyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkynyl, C<sub>5</sub>-C<sub>7</sub>  
10 cycloalkenyl, -(CH<sub>2</sub>)<sub>m</sub>-Z, or (CH<sub>2</sub>)<sub>n</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-CH<sub>3</sub>;

wherein R<sub>18</sub> is straight chained or branched C<sub>1</sub>-C<sub>6</sub> alkyl, -  
(CH<sub>2</sub>)<sub>m</sub>-Z, or (CH<sub>2</sub>)<sub>q</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-CH<sub>3</sub>;

15 wherein each R<sub>19</sub> is independently H, or straight chained  
or branched C<sub>1</sub>-C<sub>6</sub> alkyl;

wherein each R<sub>20</sub> is independently -H; straight chained or  
branched C<sub>1</sub>-C<sub>7</sub> alkyl, monofluoroalkyl or polyfluoroalkyl;  
20 straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl or alkynyl; C<sub>3</sub>-  
C<sub>7</sub> cycloalkyl or C<sub>5</sub>-C<sub>7</sub> cycloalkenyl; -F, -Cl, -Br, or -I;  
-NO<sub>2</sub>; -N<sub>3</sub>; -CN; -OR<sub>21</sub>, -OCOR<sub>21</sub>, -COR<sub>21</sub>, -NCOR<sub>21</sub>, -N(R<sub>21</sub>)<sub>2</sub>, -  
CON(R<sub>21</sub>)<sub>2</sub>, or -COOR<sub>21</sub>; aryl or heteroaryl; or two R<sub>20</sub> groups  
present on adjacent carbon atoms can join together to  
25 form a methylenedioxy group;

wherein each R<sub>21</sub> is independently -H; straight chained or  
branched C<sub>1</sub>-C<sub>7</sub> alkyl, monofluoroalkyl or polyfluoroalkyl;  
straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl or alkynyl; C<sub>3</sub>-  
30 C<sub>7</sub> cycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, aryl, or aryl(C<sub>1</sub>-  
C<sub>6</sub>)alkyl;

wherein each  $R_{22}$  is independently H, F, Cl or  $C_1-C_4$  straight chained or branched alkyl;

wherein each m is an integer from 0 to 4 inclusive;

5

wherein each n is an integer from 1 to 4 inclusive;

wherein p is an integer from 0 to 2 inclusive;

10

wherein q is an integer from 2 to 4 inclusive;

wherein t is 1 or 2;

wherein U is O,  $-NR_{16}$ , S,  $C(R_{17})_2$ , or  $-NSO_2R_{16}$ ;

15

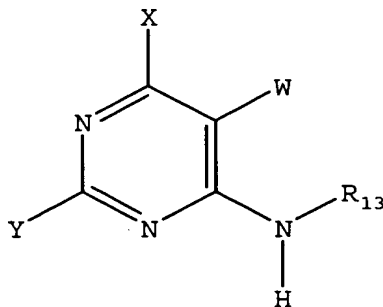
wherein Z is  $C_3-C_{10}$  cycloalkyl,  $C_4-C_7$  cyclic ether,  $C_4-C_7$  cyclic thioether, aryl, or heteroaryl; or

a pharmaceutically acceptable salt thereof.

20

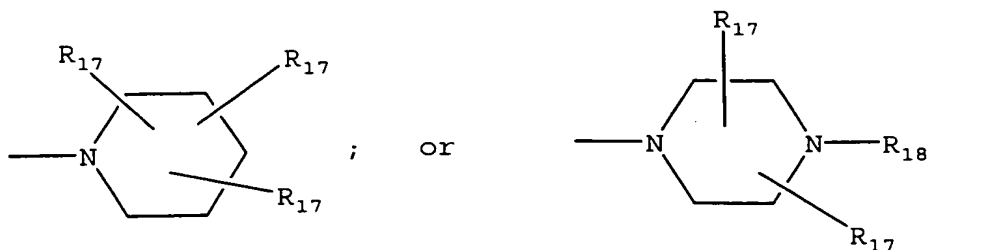
The invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound having the structure:

25



wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

wherein X is  $\text{NR}_{11}\text{R}_{12}$ ;



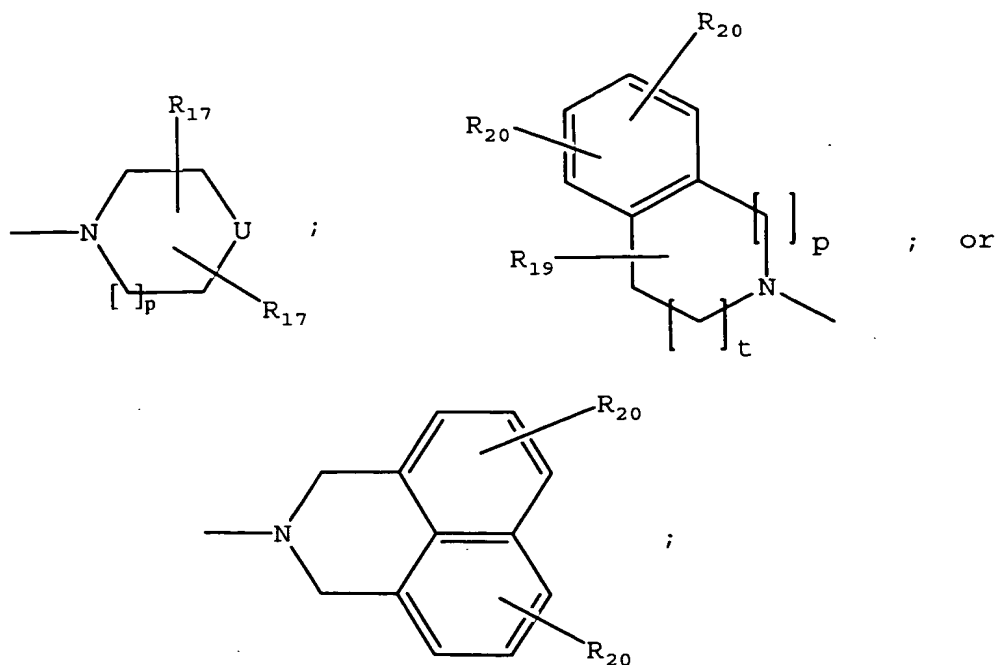
5

wherein  $\text{R}_{11}$  is H, straight chained or branched  $\text{C}_1\text{-C}_7$  alkyl,  $(\text{CH}_2)_q\text{-O-}(\text{CH}_2)_m\text{-CH}_3$ , aryl or aryl( $\text{C}_1\text{-C}_6$ )alkyl;

10    wherein  $\text{R}_{12}$  is straight chained or branched  $\text{C}_1\text{-C}_7$  alkyl,  $(\text{CH}_2)_q\text{-O-}(\text{CH}_2)_m\text{-CH}_3$ , or  $-(\text{CH}_2)_m\text{-Z}$ ;

wherein  $\text{R}_{13}$  is a bicyclic alkyl ring system, aryl or aryl( $\text{C}_1\text{-C}_6$ )alkyl;

15    wherein Y is  $\text{NR}_{14}\text{R}_{15}$ ;



wherein  $R_{14}$  is H, straight chained or branched  $C_1$ - $C_6$  alkyl,  $(CH_2)_q$ -O- $(CH_2)_m$ - $CH_3$ ,  $C_3$ - $C_6$  cycloalkyl, or  $(C(R_{19})_2)_m$ -Z;

5

wherein  $R_{15}$  is straight chained or branched  $C_3$ - $C_6$  alkyl,  $(CH_2)_q$ -O- $(CH_2)_m$ - $CH_3$ ,  $C_3$ - $C_6$  cycloalkyl, or  $(C(R_{19})_2)_m$ -Z;

wherein U is O,  $-NR_{16}$ , S,  $C(R_{17})_2$ , or  $-NSO_2R_{16}$ ;

10

wherein Z is  $C_3$ - $C_{10}$  cycloalkyl, aryl, or heteroaryl;

wherein  $R_{16}$  is straight chained or branched  $C_1$ - $C_7$  alkyl, straight chained or branched  $C_1$ - $C_7$  monofluoroalkyl, straight chained or branched  $C_1$ - $C_7$  polyfluoroalkyl, straight chained or branched  $C_2$ - $C_7$  alkenyl, straight chained or branched  $C_2$ - $C_7$  alkynyl,  $C_5$ - $C_7$  cycloalkenyl,  $-(CH_2)_m$ -Z, or  $(CH_2)_q$ -O- $(CH_2)_m$ - $CH_3$ ;

15

wherein each  $R_{17}$  is independently H;  $-OR_{21}$ ,  $-OCOR_{21}$ ,  $-COR_{21}$ ,  $-NCOR_{21}$ ,  $-N(R_{21})_2$ ,  $-CON(R_{21})_2$ ,  $-COOR_{21}$ , straight chained or branched  $C_1-C_7$  alkyl, straight chained or branched  $C_1-C_7$  monofluoroalkyl, straight chained or branched  $C_1-C_7$  polyfluoroalkyl, straight chained or branched  $C_2-C_7$  alkenyl, straight chained or branched  $C_2-C_7$  alkynyl,  $C_5-C_7$  cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_n-O-(CH_2)_m-CH_3$ ;

wherein  $R_{18}$  is straight chained or branched  $C_1-C_6$  alkyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_q-O-(CH_2)_m-CH_3$ ;

wherein each  $R_{19}$  is independently H, or straight chained or branched  $C_1-C_6$  alkyl;

wherein each  $R_{20}$  is independently -H; straight chained or branched  $C_1-C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2-C_7$  alkenyl or alkynyl;  $C_3-C_7$  cycloalkyl or  $C_5-C_7$  cycloalkenyl; -F, -Cl, -Br, or -I;  $-NO_2$ ;  $-N_3$ ; -CN;  $-OR_{21}$ ,  $-OCOR_{21}$ ,  $-COR_{21}$ ,  $-NCOR_{21}$ ,  $-N(R_{21})_2$ ,  $-CON(R_{21})_2$ , or  $-COOR_{21}$ ; aryl or heteroaryl; or two  $R_{20}$  groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each  $R_{21}$  is independently -H; straight chained or branched  $C_1-C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2-C_7$  alkenyl or alkynyl;  $C_3-C_7$  cycloalkyl,  $C_5-C_7$  cycloalkenyl, aryl or aryl( $C_1-C_6$ )alkyl;

wherein each  $m$  is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

wherein p is an integer from 0 to 2 inclusive;

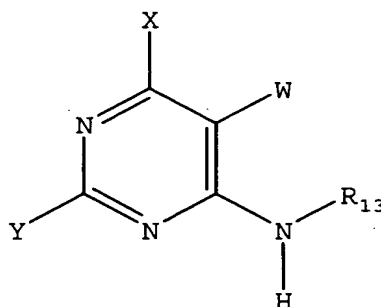
5

wherein q is an integer from 2 to 4 inclusive;

wherein t is 1 or 2; or

10 a pharmaceutically acceptable salt thereof.

The invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a  
15 compound having the structure:



20

wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

wherein X is  $N(CH_3)_2$  or

25

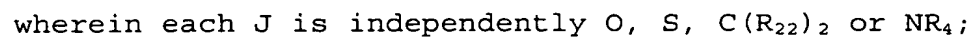


5

10 wherein  $Q_1$  is



wherein  $Q_2$  is

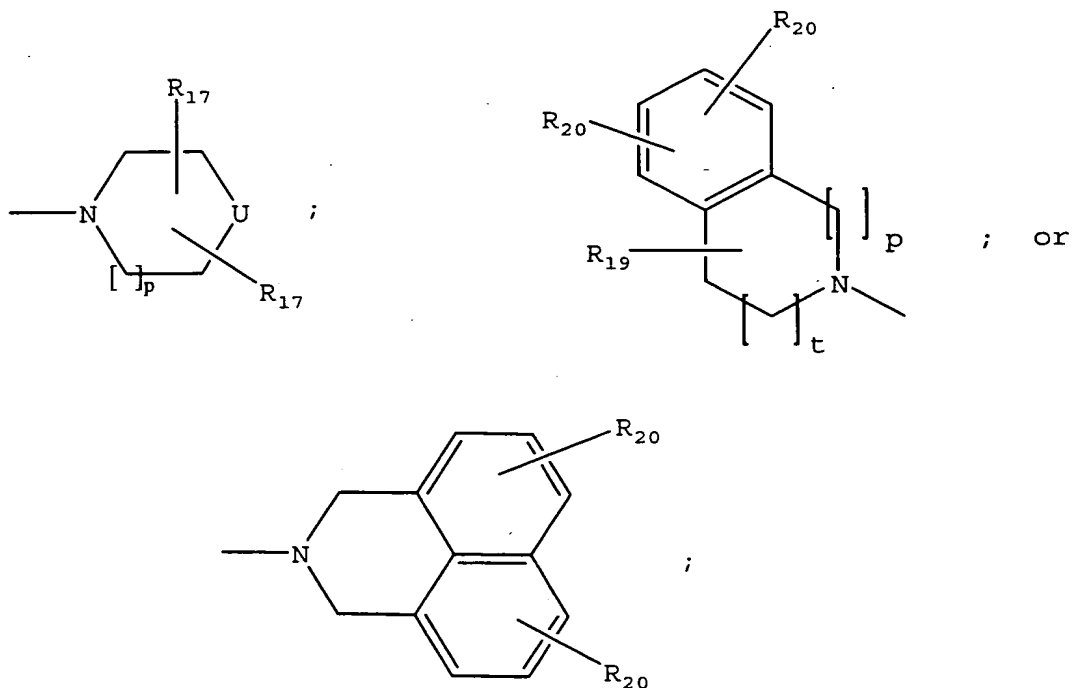




wherein  $R_4$  is -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$  cycloalkenyl or aryl;

5

wherein Y is  $NR_{14}R_{15}$ ;



10 wherein  $R_{14}$  is H, straight chained or branched  $C_1$ - $C_6$  alkyl,  $(CH_2)_q-O-(CH_2)_m-CH_3$ ,  $C_3$ - $C_6$  cycloalkyl, or  $(C(R_{19})_2)_m-Z$ ;

wherein  $R_{15}$  is straight chained or branched  $C_3$ - $C_6$  alkyl,  $(CH_2)_q-O-(CH_2)_m-CH_3$ ,  $C_3$ - $C_6$  cycloalkyl, or  $(C(R_{19})_2)_m-Z$ ;

15

wherein U is O,  $-NR_{16}$ , S,  $C(R_{17})_2$ , or  $-NSO_2R_{16}$ ;

wherein Z is  $C_3$ - $C_{10}$  cycloalkyl, aryl, or heteroaryl;

wherein  $R_{16}$  is straight chained or branched  $C_1$ - $C_7$  alkyl, straight chained or branched  $C_1$ - $C_7$  monofluoroalkyl, straight chained or branched  $C_1$ - $C_7$  polyfluoroalkyl,  
 5 straight chained or branched  $C_2$ - $C_7$  alkenyl, straight chained or branched  $C_2$ - $C_7$  alkynyl,  $C_5$ - $C_7$  cycloalkenyl, -  
 $(CH_2)_m-Z$ , or  $(CH_2)_q-O-(CH_2)_m-CH_3$ ;

wherein each  $R_{17}$  is independently H;  $-OR_{21}$ ,  $-OCOR_{21}$ ,  $-COR_{21}$ ,  
 10  $-NCOR_{21}$ ,  $-N(R_{21})_2$ ,  $-CON(R_{21})_2$ ,  $-COOR_{21}$ , straight chained or branched  $C_1$ - $C_7$  alkyl, straight chained or branched  $C_1$ - $C_7$  monofluoroalkyl, straight chained or branched  $C_1$ - $C_7$  polyfluoroalkyl, straight chained or branched  $C_2$ - $C_7$  alkenyl, straight chained or branched  $C_2$ - $C_7$  alkynyl,  $C_5$ - $C_7$   
 15 cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_n-O-(CH_2)_m-CH_3$ ;

wherein  $R_{18}$  is straight chained or branched  $C_1$ - $C_6$  alkyl, -  
 $(CH_2)_m-Z$ , or  $(CH_2)_q-O-(CH_2)_m-CH_3$ ;

20 wherein each  $R_{19}$  is independently H, or straight chained or branched  $C_1$ - $C_6$  alkyl;

wherein each  $R_{20}$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl;  
 25 straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl or  $C_5$ - $C_7$  cycloalkenyl; -F, -Cl, -Br, or -I; - $NO_2$ ; - $N_3$ ; -CN;  $-OR_{21}$ ,  $-OCOR_{21}$ ,  $-COR_{21}$ ,  $-NCOR_{21}$ ,  $-N(R_{21})_2$ ,  $-CON(R_{21})_2$ , or  $-COOR_{21}$ ; aryl or heteroaryl; or two  $R_{20}$  groups present on adjacent carbon atoms can join together to  
 30 form a methylenedioxy group;

wherein each  $R_{21}$  is independently -H; straight chained or

branched C<sub>1</sub>-C<sub>7</sub> alkyl, monofluoroalkyl or polyfluoroalkyl;  
 straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl or alkynyl; C<sub>3</sub>-  
 C<sub>7</sub> cycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, aryl or aryl(C<sub>1</sub>-  
 C<sub>6</sub>)alkyl;

5

wherein each R<sub>22</sub> is independently H, F, Cl or C<sub>1</sub>-C<sub>4</sub>  
 straight chained or branched alkyl;

wherein each m is an integer from 0 to 4 inclusive;

10

wherein each n is an integer from 1 to 4 inclusive;

wherein p is an integer from 0 to 2 inclusive;

15

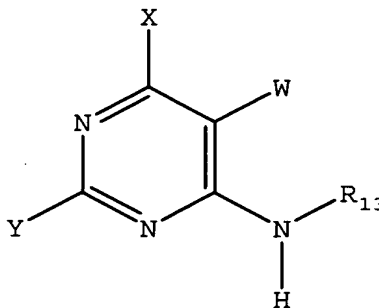
wherein q is an integer from 2 to 4 inclusive;

wherein t is 1 or 2; or

a pharmaceutically acceptable salt thereof.

20

The invention provides a pharmaceutical composition  
 comprising a pharmaceutically acceptable carrier and a  
 compound having the structure:

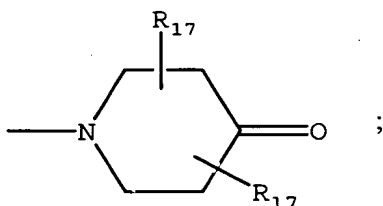


25

wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

5

wherein X is  $N(CH_3)_2$  or



10 wherein  $R_{13}$  is a bicyclic alkyl ring system, aryl or aryl( $C_1-C_6$ )alkyl;

wherein Y is  $NR_{14}R_{15}$ ;

15 wherein  $R_{14}$  is H, straight chained or branched  $C_1-C_6$  alkyl,  $(CH_2)_q-O-(CH_2)_m-CH_3$ ,  $C_3-C_6$  cycloalkyl, or  $(C(R_{19})_2)_m-Z$ ;

wherein  $R_{15}$  is  $(C(R_{19})_2)_m-N(R_{16})_2$ ;

20 wherein Z is  $C_3-C_{10}$  cycloalkyl, aryl, or heteroaryl;

wherein  $R_{16}$  is straight chained or branched  $C_1-C_7$  alkyl, straight chained or branched  $C_1-C_7$  monofluoroalkyl, straight chained or branched  $C_1-C_7$  polyfluoroalkyl,  
 25 straight chained or branched  $C_2-C_7$  alkenyl, straight chained or branched  $C_2-C_7$  alkynyl,  $C_5-C_7$  cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_q-O-(CH_2)_m-CH_3$ ;

wherein each  $R_{17}$  is independently H;  $-OR_{21}$ ,  $-OCOR_{21}$ ,  $-COR_{21}$ ,

-NCOR<sub>21</sub>, -N(R<sub>21</sub>)<sub>2</sub>, -CON(R<sub>21</sub>)<sub>2</sub>, -COOR<sub>21</sub>, straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> monofluoroalkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> polyfluoroalkyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkynyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, -(CH<sub>2</sub>)<sub>m</sub>-Z, or (CH<sub>2</sub>)<sub>n</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-CH<sub>3</sub>;

wherein each R<sub>19</sub> is independently H, or straight chained or branched C<sub>1</sub>-C<sub>6</sub> alkyl;

10

wherein each R<sub>21</sub> is independently -H; straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl or alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, aryl or aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl;

15

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

20

wherein q is an integer from 2 to 4 inclusive; or

a pharmaceutically acceptable salt thereof.

25 As used in the present invention, the term "bicyclic alkyl ring systems" includes, but is not limited to, bicyclo[2.2.1]heptane, bicyclo[3.1.1]heptane and bicyclo[2.2.2]octane. In addition, the bicyclic alkyl ring systems may be substituted with one or more of the following: -F, -NO<sub>2</sub>, -CN, straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> monofluoroalkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub>

30

polyfluoroalkyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkynyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, -N(R<sub>21</sub>)<sub>2</sub>, -OR<sub>21</sub>, -COR<sub>21</sub>, -CO<sub>2</sub>R<sub>21</sub>, -CON(R<sub>21</sub>)<sub>2</sub> or (CH<sub>2</sub>)<sub>n</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-CH<sub>3</sub>.

5

As used in the present invention, the term "cycloalkyl" includes, C<sub>3</sub>-C<sub>7</sub> cycloalkyl moieties which may be substituted with one or more of the following: -F, -NO<sub>2</sub>, -CN, straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, straight  
 10 chained or branched C<sub>1</sub>-C<sub>7</sub> monofluoroalkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> polyfluoroalkyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkynyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>3</sub>-C<sub>7</sub> monofluorocycloalkyl, C<sub>3</sub>-C<sub>7</sub> polyfluorocycloalkyl, C<sub>5</sub>-C<sub>7</sub>  
 15 cycloalkenyl, -N(R<sub>4</sub>)<sub>2</sub>, -OR<sub>4</sub>, -COR<sub>4</sub>, -NCOR<sub>4</sub>, -CO<sub>2</sub>R<sub>4</sub>, -CON(R<sub>4</sub>)<sub>2</sub> or (CH<sub>2</sub>)<sub>n</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-CH<sub>3</sub>.

As used in the present invention, the term "cyclohexyl" includes, cyclohexyl groups which may be substituted with  
 20 one or more of the following: -F, -NO<sub>2</sub>, -CN, straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> monofluoroalkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> polyfluoroalkyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub>  
 25 alkynyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>3</sub>-C<sub>7</sub> monofluorocycloalkyl, C<sub>3</sub>-C<sub>7</sub> polyfluorocycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, -N(R<sub>4</sub>)<sub>2</sub>, -OR<sub>4</sub>, -COR<sub>4</sub>, -NCOR<sub>4</sub>, -CO<sub>2</sub>R<sub>4</sub>, -CON(R<sub>4</sub>)<sub>2</sub> or (CH<sub>2</sub>)<sub>n</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-CH<sub>3</sub>.

As used in the present invention, the term "cycloalkenyl" includes, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl moieties which may be  
 30 substituted with one or more of the following: -F, -Cl, -Br, -I, -NO<sub>2</sub>, -CN, straight chained or branched C<sub>1</sub>-C<sub>7</sub>

alkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> monofluoroalkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> polyfluoroalkyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkynyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>3</sub>-C<sub>7</sub> monofluorocycloalkyl, C<sub>3</sub>-C<sub>7</sub> polyfluorocycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, -N(R<sub>4</sub>)<sub>2</sub>, -OR<sub>4</sub>, -COR<sub>4</sub>, -NCOR<sub>4</sub>, -CO<sub>2</sub>R<sub>4</sub>, -CON(R<sub>4</sub>)<sub>2</sub> or (CH<sub>2</sub>)<sub>n</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-CH<sub>3</sub>.

In the present invention, the term "heteroaryl" is used to include five and six membered unsaturated rings that may contain one or more oxygen, sulfur, or nitrogen atoms. Examples of heteroaryl groups include, but are not limited to, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, and triazinyl.

In addition the term "heteroaryl" is used to include fused bicyclic ring systems that may contain one or more heteroatoms such as oxygen, sulfur and nitrogen. Examples of such heteroaryl groups include, but are not limited to, indoliziny, indolyl, isoindolyl, benzo[b]furanyl, benzo[b]thiophenyl, indazolyl, benzimidazolyl, purinyl, benzoxazolyl, benzisoxazolyl, benzo[b]thiazolyl, imidazo[2,1-b]thiazolyl, cinnolinyl, quinazolinyl, quinoxalinyl, 1,8-naphthyridinyl, pteridinyl, quinolinyl, isoquinolinyl, phthalimidyl and 2,1,3-benzothiazolyl.

The term "heteroaryl" also includes those chemical moieties recited above which may be substituted with one or more of the following: -F, -Cl, -Br, -I, -NO<sub>2</sub>, -CN,

straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> monofluoroalkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> polyfluoroalkyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkynyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>3</sub>-C<sub>7</sub> monofluorocycloalkyl, C<sub>3</sub>-C<sub>7</sub> polyfluorocycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, -N(R<sub>4</sub>)<sub>2</sub>, -OR<sub>4</sub>, -COR<sub>4</sub>, -NCOR<sub>4</sub>, -CO<sub>2</sub>R<sub>4</sub>, -CON(R<sub>4</sub>)<sub>2</sub> or (CH<sub>2</sub>)<sub>n</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-CH<sub>3</sub>.

The term "heteroaryl" further includes the N-oxides of those chemical moieties recited above which include at least one nitrogen atom.

In the present invention the term "aryl" is phenyl or naphthyl. The term "aryl" also includes phenyl and naphthyl which may be substituted with one or more of the following: -F, -Cl, -Br, -I, -NO<sub>2</sub>, -CN, straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> monofluoroalkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> polyfluoroalkyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkynyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>3</sub>-C<sub>7</sub> monofluorocycloalkyl, C<sub>3</sub>-C<sub>7</sub> polyfluorocycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, -N(R<sub>4</sub>)<sub>2</sub>, -OR<sub>4</sub>, -SR<sub>4</sub>, -OCOR<sub>4</sub>, -COR<sub>4</sub>, -NCOR<sub>4</sub>, -CO<sub>2</sub>R<sub>4</sub>, -CON(R<sub>4</sub>)<sub>2</sub> or (CH<sub>2</sub>)<sub>n</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-CH<sub>3</sub>.

25

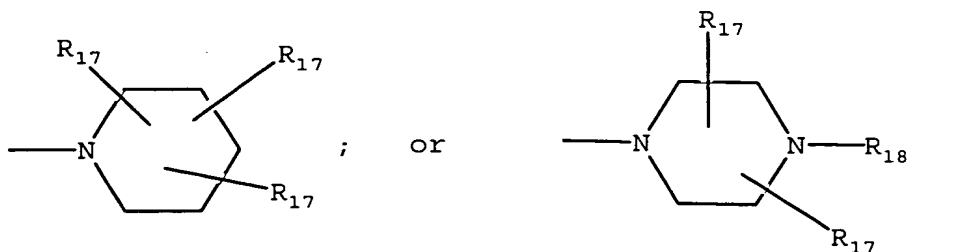
In one embodiment of any of the pharmaceutical compositions described herein, the compound is enantiomerically and diasteriomERICALLY pure. In one embodiment the compound is enantiomerically or diasteriomERICALLY pure.

30



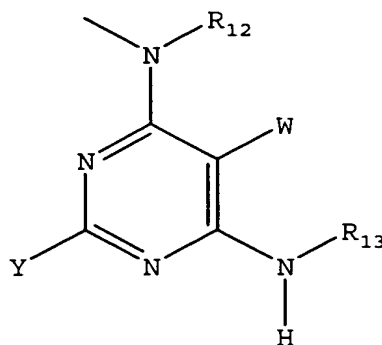
In one embodiment of any of the pharmaceutical compositions described herein, the compound can be administered orally.

5 In one embodiment, X is:



In one embodiment, X is  $\text{NR}_{11}\text{R}_{12}$  and  $\text{R}_{11}$  is H or straight  
15 chained or branched  $\text{C}_1\text{-C}_7$  alkyl.

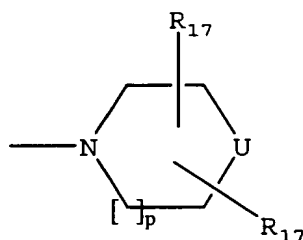
In one embodiment, the compound has the structure:



In one embodiment,  $R_{13}$  is a bicyclic alkyl ring system, cyclohexyl or aryl.

In one embodiment,  $R_{14}$  is H, straight chained or branched  
 5  $C_1-C_6$  alkyl or  $(CH_2)_q-O-(CH_2)_m-CH_3$ .

In one embodiment, Y is



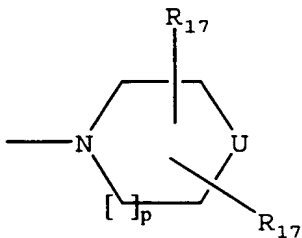
10 In one embodiment, U is  $NR_{16}$ .

In one embodiment,  $R_{16}$  is  $(CH_2)_m-Z$ .

In one embodiment, Z is aryl or heteroaryl.

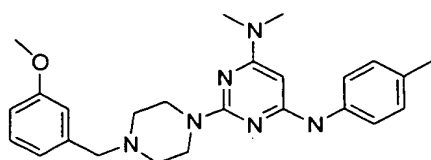
15

In one embodiment, Y is

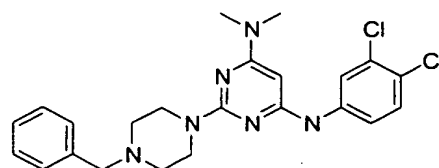


20 In one embodiment, U is  $NR_{16}$ .

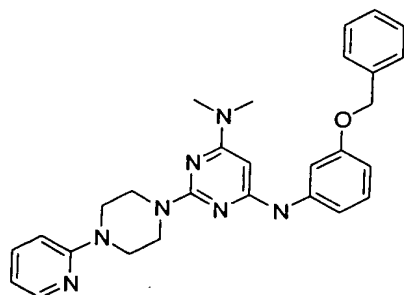
In one embodiment, the compound is selected from the  
 5 group consisting of:



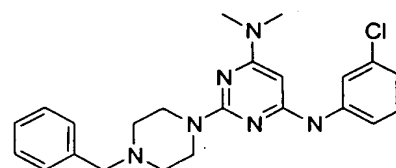
;



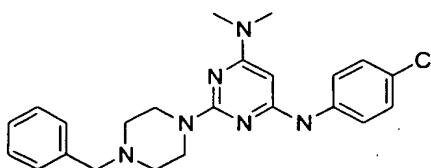
;



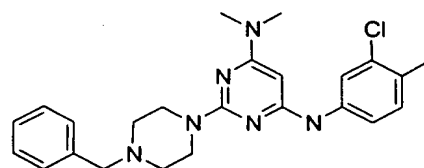
;



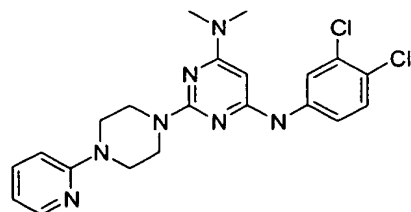
;



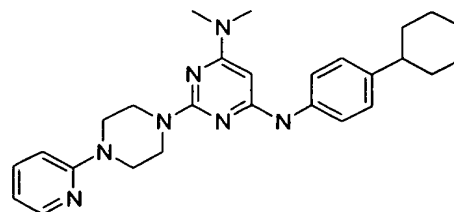
;



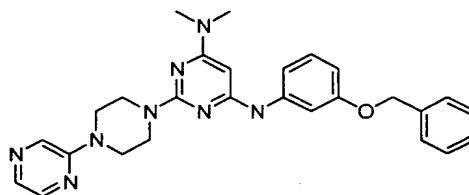
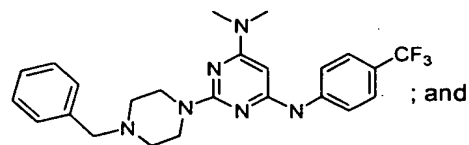
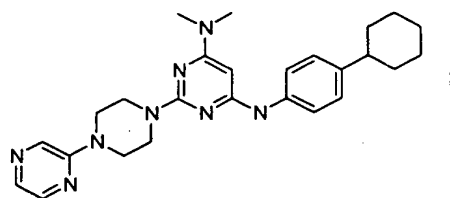
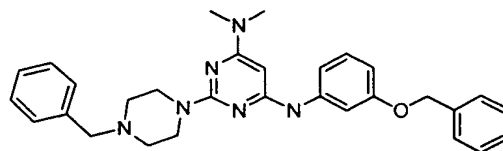
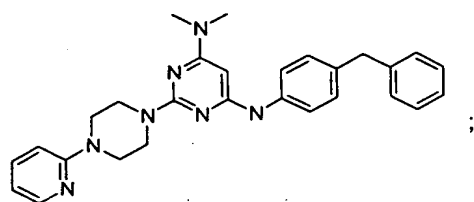
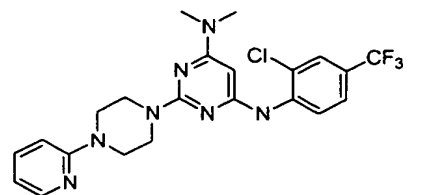
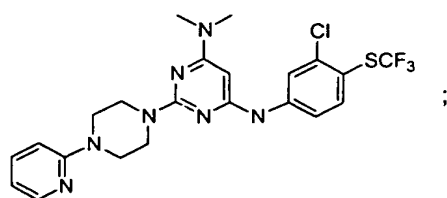
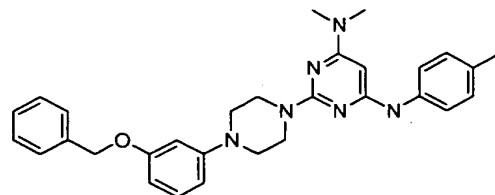
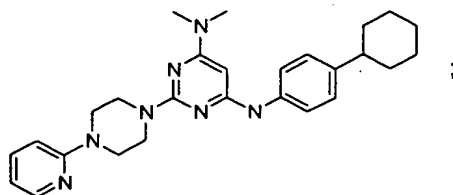
;



; and

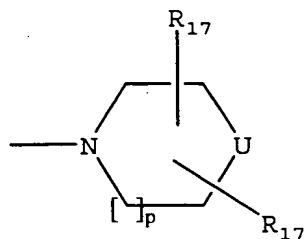


In one embodiment, compound is selected from the group consisting of:



In one embodiment, X is  $N(CH_3)_2$ .

In one embodiment, Y is



5

In one embodiment,  $R_{13}$  is an aryl substituted with a  $C_1$ - $C_{10}$  straight chained alkyl.

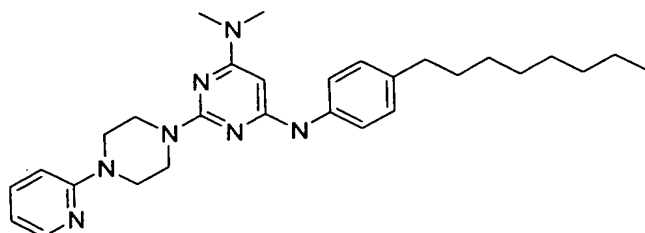
10

15

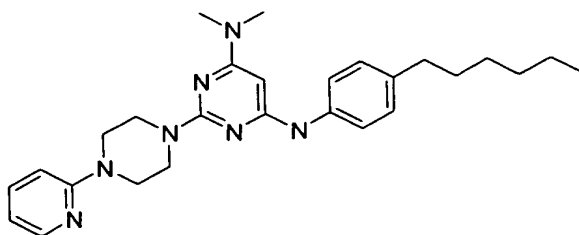
20

25

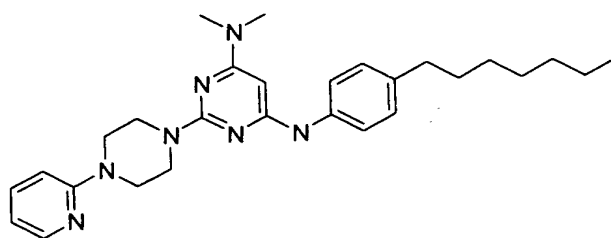
In one embodiment, the compound is selected from a group consisting of:



;



; and

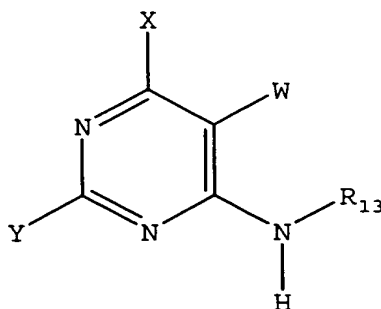


5

10

15

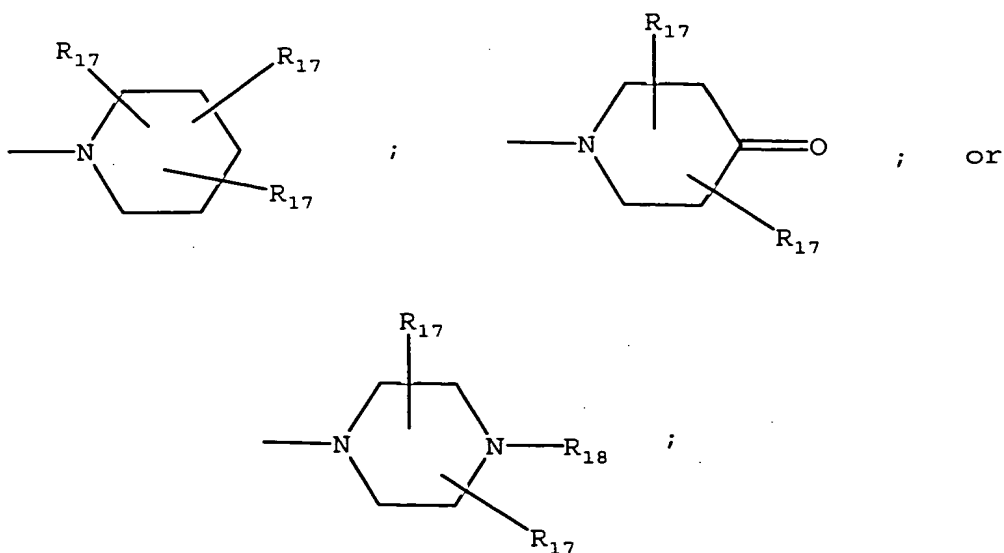
The invention provides a compound having the structure:



wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

5

wherein X is;  $\text{NR}_{11}\text{R}_{12}$ ;



wherein  $\text{R}_{11}$  is H, straight chained or branched  $\text{C}_1\text{-C}_7$  alkyl,  $(\text{CH}_2)_q\text{-O-(CH}_2)_m\text{-CH}_3$ , aryl, or aryl  $(\text{C}_1\text{-C}_6)$  alkyl;

10

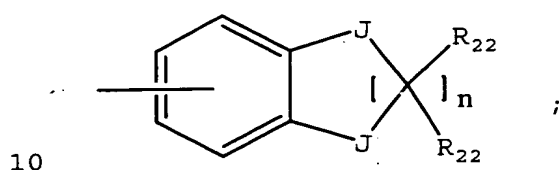
wherein  $\text{R}_{12}$  is straight chained or branched  $\text{C}_1\text{-C}_7$  alkyl,  $(\text{CH}_2)_q\text{-O-(CH}_2)_m\text{-CH}_3$ , or  $-(\text{CH}_2)_m\text{-Z}$ ;

wherein  $\text{R}_{13}$  is a bicyclic alkyl ring system, adamantyl,

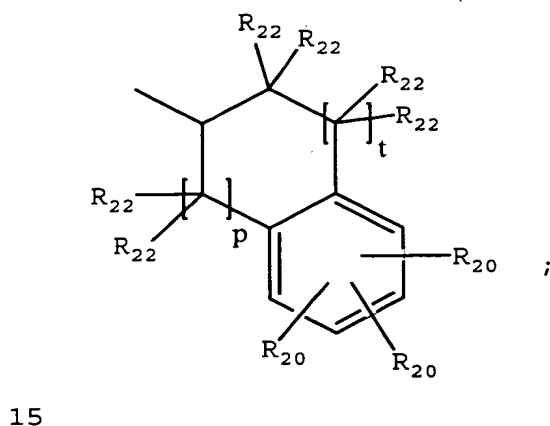
noradamantyl, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, heteroaryl, aryl, aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl, Q<sub>1</sub> or Q<sub>2</sub>;

wherein aryl may be substituted with one or more C<sub>1</sub>-C<sub>10</sub>  
 5 straight chained or branched alkyl, aryl, heteroaryl, or  
 N(R<sub>19</sub>)-Z;

wherein Q<sub>1</sub> is



wherein Q<sub>2</sub> is

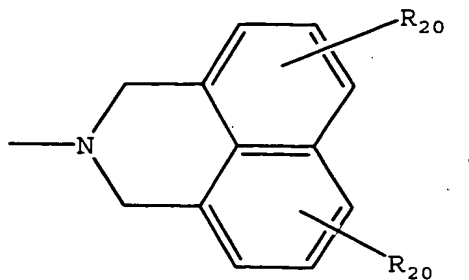
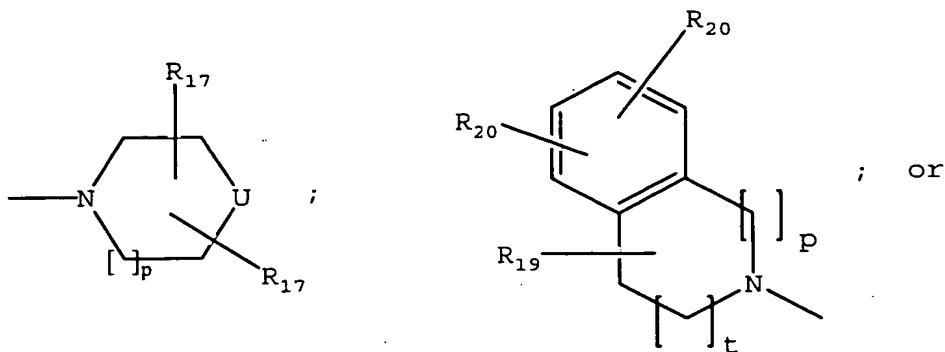


wherein each J is independently O, S, C(R<sub>22</sub>)<sub>2</sub> or NR<sub>4</sub>;

wherein R<sub>4</sub> is H; straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl,  
 monofluoroalkyl or polyfluoroalkyl; straight chained or  
 20 branched C<sub>2</sub>-C<sub>7</sub> alkenyl or alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>5</sub>-C<sub>7</sub>  
 cycloalkenyl or aryl;



wherein Y is  $\text{NR}_{14}\text{R}_{15}$ ;



5

wherein  $\text{R}_{14}$  is H, straight chained or branched  $\text{C}_1\text{-C}_6$  alkyl,  $(\text{CH}_2)_q\text{-O-(CH}_2)_m\text{-CH}_3$ ,  $\text{C}_3\text{-C}_6$  cycloalkyl, or  $(\text{C}(\text{R}_{19})_2)_m\text{-Z}$ ;

- 10 wherein  $\text{R}_{15}$  is straight chained or branched  $\text{C}_3\text{-C}_6$  alkyl,  $(\text{CH}_2)_q\text{-O-(CH}_2)_m\text{-CH}_3$ ,  $\text{C}_3\text{-C}_6$  cycloalkyl,  $(\text{C}(\text{R}_{19})_2)_m\text{N}(\text{R}_{16})_2$  or  $(\text{C}(\text{R}_{19})_2)_m\text{-Z}$ ;

- wherein  $\text{R}_{16}$  is straight chained or branched  $\text{C}_1\text{-C}_7$  alkyl,  
 15 straight chained or branched  $\text{C}_1\text{-C}_7$  monofluoroalkyl,  
 straight chained or branched  $\text{C}_1\text{-C}_7$  polyfluoroalkyl,  
 straight chained or branched  $\text{C}_2\text{-C}_7$  alkenyl, straight  
 chained or branched  $\text{C}_2\text{-C}_7$  alkynyl,  $\text{C}_5\text{-C}_7$  cycloalkenyl, -  
 $(\text{CH}_2)_m\text{-Z}$ , or  $(\text{CH}_2)_q\text{-O-(CH}_2)_m\text{-CH}_3$ ;

20

wherein each  $R_{17}$  is independently H;  $-OR_{21}$ ,  $-OCOR_{21}$ ,  $-COR_{21}$ ,  $-NCOR_{21}$ ,  $-N(R_{21})_2$ ,  $-CON(R_{21})_2$ ,  $-COOR_{21}$ , straight chained or branched  $C_1$ - $C_7$  alkyl, straight chained or branched  $C_1$ - $C_7$  monofluoroalkyl, straight chained or branched  $C_1$ - $C_7$  polyfluoroalkyl, straight chained or branched  $C_2$ - $C_7$  alkenyl, straight chained or branched  $C_2$ - $C_7$  alkynyl,  $C_5$ - $C_7$  cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_n-O-(CH_2)_m-CH_3$ ;

wherein  $R_{18}$  is straight chained or branched  $C_1$ - $C_6$  alkyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_q-O-(CH_2)_m-CH_3$ ;

wherein each  $R_{19}$  is independently H, or straight chained or branched  $C_1$ - $C_6$  alkyl;

wherein each  $R_{20}$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl or  $C_5$ - $C_7$  cycloalkenyl; -F, -Cl, -Br, or -I;  $-NO_2$ ;  $-N_3$ ; -CN;  $-OR_{21}$ ,  $-OCOR_{21}$ ,  $-COR_{21}$ ,  $-NCOR_{21}$ ,  $-N(R_{21})_2$ ,  $-CON(R_{21})_2$ , or  $-COOR_{21}$ ; aryl or heteroaryl; or two  $R_{20}$  groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each  $R_{21}$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$  cycloalkenyl, aryl, or aryl( $C_1$ - $C_6$ )alkyl;

wherein each  $R_{22}$  is independently H, F, Cl or  $C_1$ - $C_4$  straight chained or branched alkyl;

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

5 wherein p is an integer from 0 to 2 inclusive;

wherein q is an integer from 2 to 4 inclusive;

wherein t is 1 or 2;

10

wherein U is O,  $-NR_{16}$ , S,  $C(R_{17})_2$ , or  $-NSO_2R_{16}$ ;

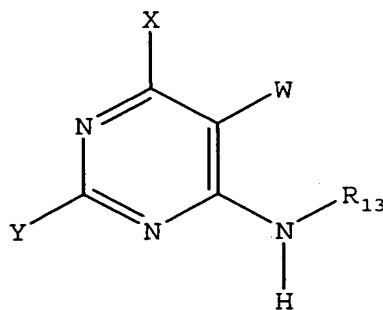
wherein Z is  $C_3$ - $C_{10}$  cycloalkyl,  $C_4$ - $C_7$  cyclic ether,  $C_4$ - $C_7$  cyclic thioether, aryl, or heteroaryl; or

15

a pharmaceutically acceptable salt thereof.

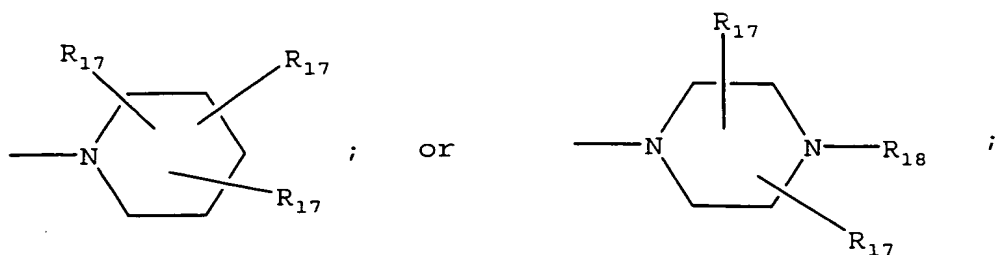
The invention provides a compound having the structure:

20



wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

wherein X is  $\text{NR}_{11}\text{R}_{12}$ ;



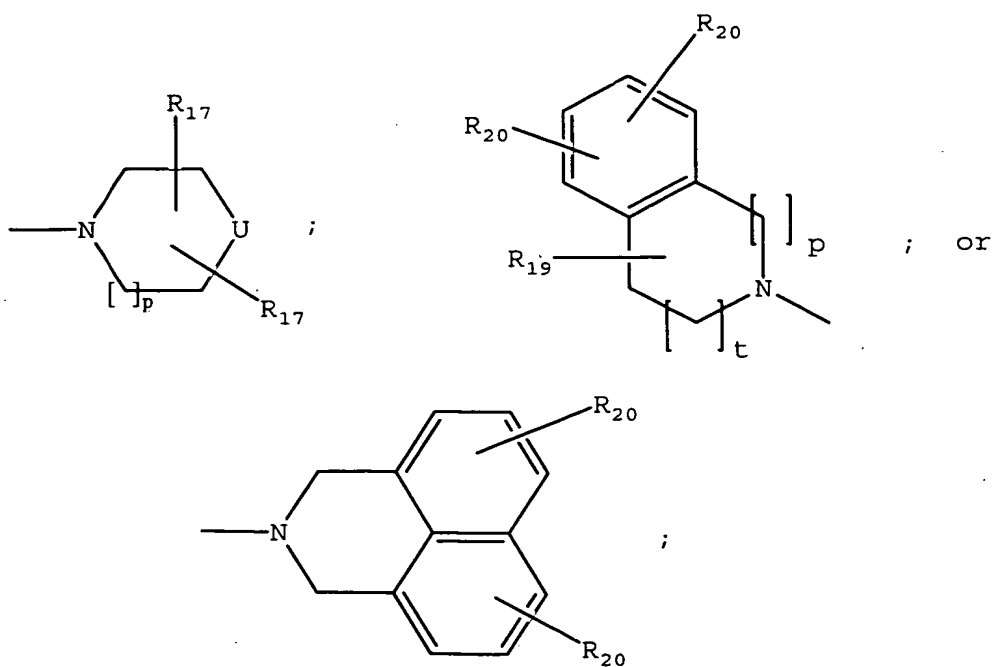
wherein  $\text{R}_{11}$  is H, straight chained or branched  $\text{C}_1\text{-C}_7$  alkyl,  $(\text{CH}_2)_q\text{-O-(CH}_2)_m\text{-CH}_3$ , aryl or aryl( $\text{C}_1\text{-C}_6$ )alkyl;

5

wherein  $\text{R}_{12}$  is straight chained or branched  $\text{C}_1\text{-C}_7$  alkyl,  $(\text{CH}_2)_q\text{-O-(CH}_2)_m\text{-CH}_3$ , or  $-(\text{CH}_2)_m\text{-Z}$ ;

wherein  $\text{R}_{13}$  is a bicyclic alkyl ring system, aryl or  
 10 aryl( $\text{C}_1\text{-C}_6$ )alkyl;

wherein Y is  $\text{NR}_{14}\text{R}_{15}$ ;



wherein  $R_{14}$  is H, straight chained or branched  $C_1$ - $C_6$  alkyl,  $(CH_2)_q$ -O- $(CH_2)_m$ -CH<sub>3</sub>,  $C_3$ - $C_6$  cycloalkyl, or  $(C(R_{19})_2)_m$ -Z;

5

wherein  $R_{15}$  is straight chained or branched  $C_3$ - $C_6$  alkyl,  $(CH_2)_q$ -O- $(CH_2)_m$ -CH<sub>3</sub>,  $C_3$ - $C_6$  cycloalkyl, or  $(C(R_{19})_2)_m$ -Z;

wherein U is O, -NR<sub>16</sub>, S, C(R<sub>17</sub>)<sub>2</sub>, or -NSO<sub>2</sub>R<sub>16</sub>;

10

wherein Z is  $C_3$ - $C_{10}$  cycloalkyl, aryl, or heteroaryl;

wherein  $R_{16}$  is straight chained or branched  $C_1$ - $C_7$  alkyl, straight chained or branched  $C_1$ - $C_7$  monofluoroalkyl, straight chained or branched  $C_1$ - $C_7$  polyfluoroalkyl, straight chained or branched  $C_2$ - $C_7$  alkenyl, straight chained or branched  $C_2$ - $C_7$  alkynyl,  $C_5$ - $C_7$  cycloalkenyl, -  
 (CH<sub>2</sub>)<sub>m</sub>-Z, or (CH<sub>2</sub>)<sub>q</sub>-O- $(CH_2)_m$ -CH<sub>3</sub>;

15

wherein each  $R_{17}$  is independently H;  $-OR_{21}$ ,  $-OCOR_{21}$ ,  $-COR_{21}$ ,  $-NCOR_{21}$ ,  $-N(R_{21})_2$ ,  $-CON(R_{21})_2$ ,  $-COOR_{21}$ , straight chained or branched  $C_1$ - $C_7$  alkyl, straight chained or branched  $C_1$ - $C_7$  monofluoroalkyl, straight chained or branched  $C_1$ - $C_7$  polyfluoroalkyl, straight chained or branched  $C_2$ - $C_7$  alkenyl, straight chained or branched  $C_2$ - $C_7$  alkynyl,  $C_5$ - $C_7$  cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_n-O-(CH_2)_m-CH_3$ ;

wherein  $R_{18}$  is straight chained or branched  $C_1$ - $C_6$  alkyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_q-O-(CH_2)_m-CH_3$ ;

wherein each  $R_{19}$  is independently H, or straight chained or branched  $C_1$ - $C_6$  alkyl;

wherein each  $R_{20}$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl or  $C_5$ - $C_7$  cycloalkenyl; -F, -Cl, -Br, or -I;  $-NO_2$ ;  $-N_3$ ; -CN;  $-OR_{21}$ ,  $-OCOR_{21}$ ,  $-COR_{21}$ ,  $-NCOR_{21}$ ,  $-N(R_{21})_2$ ,  $-CON(R_{21})_2$ , or  $-COOR_{21}$ ; aryl or heteroaryl; or two  $R_{20}$  groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each  $R_{21}$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$  cycloalkenyl, aryl or aryl( $C_1$ - $C_6$ )alkyl;

wherein each  $m$  is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

wherein p is an integer from 0 to 2 inclusive;

5

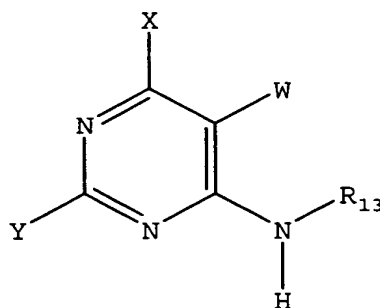
wherein q is an integer from 2 to 4 inclusive;

wherein t is 1 or 2; or

10 a pharmaceutically acceptable salt thereof.

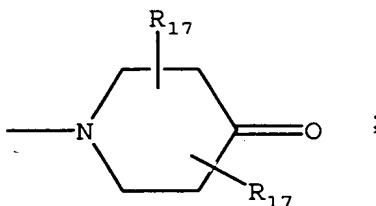
The invention provides a compound having the structure:

15



wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

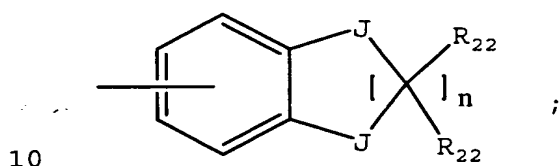
20 wherein X is  $N(CH_3)_2$  or



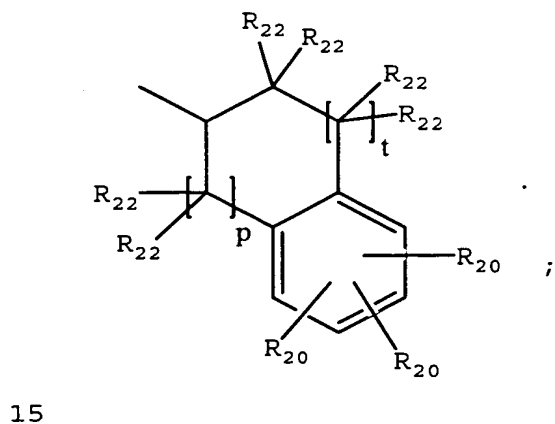
wherein  $R_{13}$  is an aryl, adamantyl, noradamantyl,  $C_3$ - $C_{10}$  cycloalkyl, heteroaryl,  $Q_1$  or  $Q_2$ ;

wherein aryl may be substituted with one or more  $C_1$ - $C_{10}$   
 5 straight chained or branched alkyl, aryl, heteroaryl, or  $N(R_{19})-Z$ ;

wherein  $Q_1$  is



wherein  $Q_2$  is

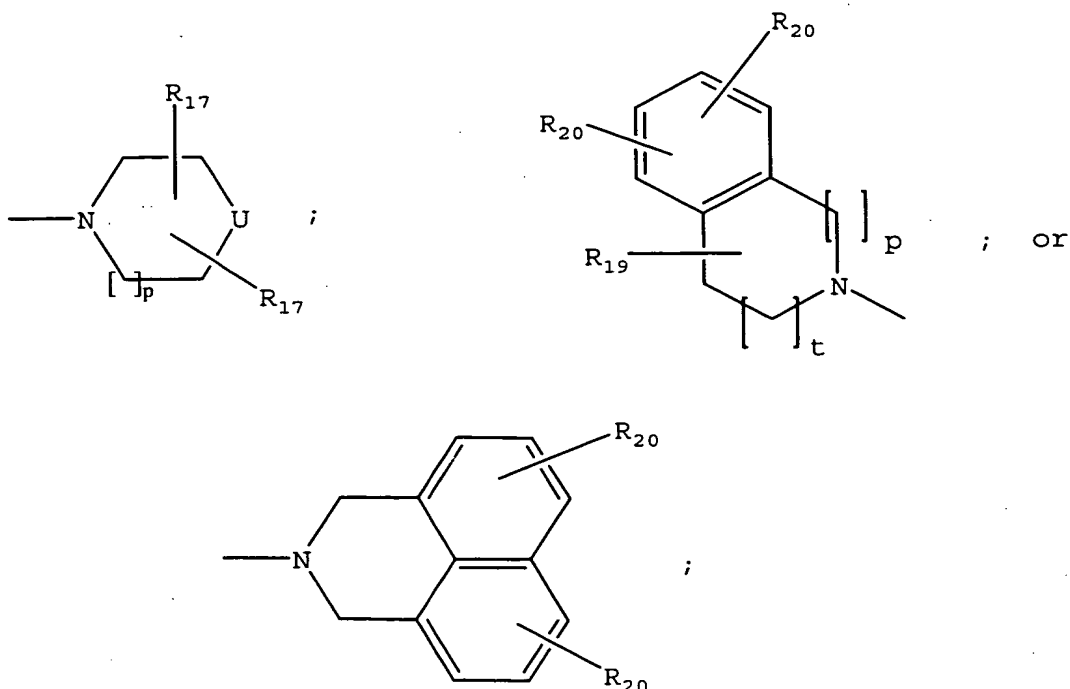


wherein each J is independently O, S,  $C(R_{22})_2$  or  $NR_4$ ;

wherein  $R_4$  is -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight  
 20 chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$  cycloalkenyl or aryl;



wherein Y is  $\text{NR}_{14}\text{R}_{15}$ ;



- 5 wherein  $\text{R}_{14}$  is H, straight chained or branched  $\text{C}_1\text{-C}_6$  alkyl,  $(\text{CH}_2)_q\text{-O-(CH}_2)_m\text{-CH}_3$ ,  $\text{C}_3\text{-C}_6$  cycloalkyl, or  $(\text{C}(\text{R}_{19})_2)_m\text{-Z}$ ;

wherein  $\text{R}_{15}$  is straight chained or branched  $\text{C}_3\text{-C}_6$  alkyl,  $(\text{CH}_2)_q\text{-O-(CH}_2)_m\text{-CH}_3$ ,  $\text{C}_3\text{-C}_6$  cycloalkyl, or  $(\text{C}(\text{R}_{19})_2)_m\text{-Z}$ ;

10

wherein U is O,  $\text{-NR}_{16}$ , S,  $\text{C}(\text{R}_{17})_2$ , or  $\text{-NSO}_2\text{R}_{16}$ ;

wherein Z is  $\text{C}_3\text{-C}_{10}$  cycloalkyl, aryl, or heteroaryl;

- 15 wherein  $\text{R}_{16}$  is straight chained or branched  $\text{C}_1\text{-C}_7$  alkyl, straight chained or branched  $\text{C}_1\text{-C}_7$  monofluoroalkyl, straight chained or branched  $\text{C}_1\text{-C}_7$  polyfluoroalkyl, straight chained or branched  $\text{C}_2\text{-C}_7$  alkenyl, straight

chained or branched  $C_2$ - $C_7$  alkynyl,  $C_5$ - $C_7$  cycloalkenyl, -  
 $(CH_2)_m-Z$ , or  $(CH_2)_q-O-(CH_2)_m-CH_3$ ;

wherein each  $R_{17}$  is independently H;  $-OR_{21}$ ,  $-OCOR_{21}$ ,  $-COR_{21}$ ,  
 5  $-NCOR_{21}$ ,  $-N(R_{21})_2$ ,  $-CON(R_{21})_2$ ,  $-COOR_{21}$ , straight chained or  
 branched  $C_1$ - $C_7$  alkyl, straight chained or branched  $C_1$ - $C_7$   
 monofluoroalkyl, straight chained or branched  $C_1$ - $C_7$   
 polyfluoroalkyl, straight chained or branched  $C_2$ - $C_7$   
 alkenyl, straight chained or branched  $C_2$ - $C_7$  alkynyl,  $C_5$ - $C_7$   
 10 cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_n-O-(CH_2)_m-CH_3$ ;

wherein  $R_{18}$  is straight chained or branched  $C_1$ - $C_6$  alkyl, -  
 $(CH_2)_m-Z$ , or  $(CH_2)_q-O-(CH_2)_m-CH_3$ ;

15 wherein each  $R_{19}$  is independently H, or straight chained  
 or branched  $C_1$ - $C_6$  alkyl;

wherein each  $R_{20}$  is independently -H; straight chained or  
 branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl;  
 20 straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ -  
 $C_7$  cycloalkyl or  $C_5$ - $C_7$  cycloalkenyl; -F, -Cl, -Br, or -I;  
 - $NO_2$ ; - $N_3$ ; -CN;  $-OR_{21}$ ,  $-OCOR_{21}$ ,  $-COR_{21}$ ,  $-NCOR_{21}$ ,  $-N(R_{21})_2$ , -  
 $CON(R_{21})_2$ , or  $-COOR_{21}$ ; aryl or heteroaryl; or two  $R_{20}$  groups  
 present on adjacent carbon atoms can join together to  
 25 form a methylenedioxy group;

wherein each  $R_{21}$  is independently -H; straight chained or  
 branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl;  
 straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ -  
 30  $C_7$  cycloalkyl,  $C_5$ - $C_7$  cycloalkenyl, aryl or aryl( $C_1$ -  
 $C_6$ )alkyl;

wherein each  $R_{22}$  is independently H, F, Cl or  $C_1$ - $C_4$  straight chained or branched alkyl;

wherein each m is an integer from 0 to 4 inclusive;

5

wherein each n is an integer from 1 to 4 inclusive;

wherein p is an integer from 0 to 2 inclusive;

10

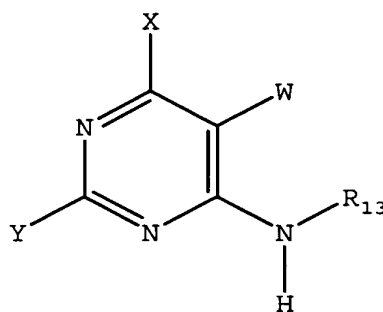
wherein q is an integer from 2 to 4 inclusive;

wherein t is 1 or 2; or

a pharmaceutically acceptable salt thereof.

15

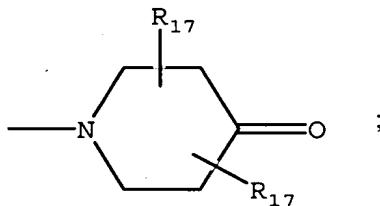
The invention provides a compound having the structure:



wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

20

wherein X is  $N(CH_3)_2$  or



wherein  $R_{13}$  is a bicyclic alkyl ring system, aryl or aryl( $C_1-C_6$ )alkyl;

5 wherein Y is  $NR_{14}R_{15}$ ;

wherein  $R_{14}$  is H, straight chained or branched  $C_1-C_6$  alkyl,  $(CH_2)_q-O-(CH_2)_m-CH_3$ ,  $C_3-C_6$  cycloalkyl, or  $(C(R_{19})_2)_m-Z$ ;

10 wherein  $R_{15}$  is  $(C(R_{19})_2)_m-N(R_{16})_2$ ;

wherein Z is  $C_3-C_{10}$  cycloalkyl, aryl, or heteroaryl;

wherein  $R_{16}$  is straight chained or branched  $C_1-C_7$  alkyl,  
 15 straight chained or branched  $C_1-C_7$  monofluoroalkyl,  
 straight chained or branched  $C_1-C_7$  polyfluoroalkyl,  
 straight chained or branched  $C_2-C_7$  alkenyl, straight  
 chained or branched  $C_2-C_7$  alkynyl,  $C_5-C_7$  cycloalkenyl, -  
 $(CH_2)_m-Z$ , or  $(CH_2)_q-O-(CH_2)_m-CH_3$ ;

20

wherein each  $R_{17}$  is independently H;  $-OR_{21}$ ,  $-OCOR_{21}$ ,  $-COR_{21}$ ,  
 $-NCOR_{21}$ ,  $-N(R_{21})_2$ ,  $-CON(R_{21})_2$ ,  $-COOR_{21}$ , straight chained or  
 branched  $C_1-C_7$  alkyl, straight chained or branched  $C_1-C_7$   
 monofluoroalkyl, straight chained or branched  $C_1-C_7$   
 25 polyfluoroalkyl, straight chained or branched  $C_2-C_7$   
 alkenyl, straight chained or branched  $C_2-C_7$  alkynyl,  $C_5-C_7$   
 cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_n-O-(CH_2)_m-CH_3$ ;

wherein each  $R_{19}$  is independently H, or straight chained  
 30 or branched  $C_1-C_6$  alkyl;

wherein each  $R_{21}$  is independently -H; straight chained or

branched C<sub>1</sub>-C<sub>7</sub> alkyl, monofluoroalkyl or polyfluoroalkyl;  
 straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl or alkynyl; C<sub>3</sub>-  
 C<sub>7</sub> cycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, aryl or aryl(C<sub>1</sub>-  
 C<sub>6</sub>)alkyl;

5

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

10

wherein q is an integer from 2 to 4 inclusive; or

a pharmaceutically acceptable salt thereof.

As used in the present invention, the term "bicyclic  
 15 alkyl ring systems" includes, but is not limited to,  
 bicyclo[2.2.1]heptane, bicyclo[3.1.1]heptane and  
 bicyclo[2.2.2]octane. In addition, the bicyclic alkyl  
 ring systems may be substituted with one or more of the  
 following: -F, -NO<sub>2</sub>, -CN, straight chained or branched  
 20 C<sub>1</sub>-C<sub>7</sub> alkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub>  
 monofluoroalkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub>  
 polyfluoroalkyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub>  
 alkenyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkynyl, C<sub>3</sub>-C<sub>7</sub>  
 cycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, -N(R<sub>21</sub>)<sub>2</sub>, -OR<sub>21</sub>, -COR<sub>21</sub>, -  
 25 CO<sub>2</sub>R<sub>21</sub>, -CON(R<sub>21</sub>)<sub>2</sub> or (CH<sub>2</sub>)<sub>n</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-CH<sub>3</sub>.

As used in the present invention, the term "cycloalkyl"  
 includes, C<sub>3</sub>-C<sub>7</sub> cycloalkyl moieties which may be  
 substituted with one or more of the following: -F, -NO<sub>2</sub>,  
 30 -CN, straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, straight  
 chained or branched C<sub>1</sub>-C<sub>7</sub> monofluoroalkyl, straight  
 chained or branched C<sub>1</sub>-C<sub>7</sub> polyfluoroalkyl, straight

chained or branched  $C_2-C_7$  alkenyl, straight chained or branched  $C_2-C_7$  alkynyl,  $C_3-C_7$  cycloalkyl,  $C_3-C_7$  monofluorocycloalkyl,  $C_3-C_7$  polyfluorocycloalkyl,  $C_5-C_7$  cycloalkenyl,  $-N(R_4)_2$ ,  $-OR_4$ ,  $-COR_4$ ,  $-NCOR_4$ ,  $-CO_2R_4$ ,   
 5  $CON(R_4)_2$  or  $(CH_2)_n-O-(CH_2)_m-CH_3$ .

As used in the present invention, the term "cyclohexyl" includes, cyclohexyl groups which may be substituted with one or more of the following:  $-F$ ,  $-NO_2$ ,  $-CN$ , straight   
 10 chained or branched  $C_1-C_7$  alkyl, straight chained or branched  $C_1-C_7$  monofluoroalkyl, straight chained or branched  $C_1-C_7$  polyfluoroalkyl, straight chained or branched  $C_2-C_7$  alkenyl, straight chained or branched  $C_2-C_7$  alkynyl,  $C_3-C_7$  cycloalkyl,  $C_3-C_7$  monofluorocycloalkyl,  $C_3-C_7$    
 15 polyfluorocycloalkyl,  $C_5-C_7$  cycloalkenyl,  $-N(R_4)_2$ ,  $-OR_4$ ,  $-COR_4$ ,  $-NCOR_4$ ,  $-CO_2R_4$ ,  $-CON(R_4)_2$  or  $(CH_2)_n-O-(CH_2)_m-CH_3$ .

As used in the present invention, the term "cycloalkenyl" includes,  $C_5-C_7$  cycloalkenyl moieties which may be substituted with one or more of the following:  $-F$ ,  $-Cl$ ,  $-Br$ ,  $-I$ ,  $-NO_2$ ,  $-CN$ , straight chained or branched  $C_1-C_7$    
 20 alkyl, straight chained or branched  $C_1-C_7$  monofluoroalkyl, straight chained or branched  $C_1-C_7$  polyfluoroalkyl, straight chained or branched  $C_2-C_7$  alkenyl, straight chained or branched  $C_2-C_7$  alkynyl,  $C_3-C_7$  cycloalkyl,  $C_3-C_7$  monofluorocycloalkyl,  $C_3-C_7$  polyfluorocycloalkyl,  $C_5-C_7$    
 25 cycloalkenyl,  $-N(R_4)_2$ ,  $-OR_4$ ,  $-COR_4$ ,  $-NCOR_4$ ,  $-CO_2R_4$ ,  $-CON(R_4)_2$  or  $(CH_2)_n-O-(CH_2)_m-CH_3$ .

30 In the present invention, the term "heteroaryl" is used to include five and six membered unsaturated rings that may contain one or more oxygen, sulfur, or nitrogen

atoms. Examples of heteroaryl groups include, but are not limited to, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, 5 pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, and triazinyl.

In addition the term "heteroaryl" is used to include fused bicyclic ring systems that may contain one or more 10 heteroatoms such as oxygen, sulfur and nitrogen. Examples of such heteroaryl groups include, but are not limited to, indolizinyl, indolyl, isoindolyl, benzo[b]furanyl, benzo[b]thiophenyl, indazolyl, benzimidazolyl, purinyl, benzoxazolyl, benzisoxazolyl, benzo[b]thiazolyl, 15 imidazo[2,1-b]thiazolyl, cinnolinyl, quinazolinyl, quinoxalinyl, 1,8-naphthyridinyl, pteridinyl, quinolinyl, isoquinolinyl, phthalimidyl and 2,1,3-benzothiazolyl.

The term "heteroaryl" also includes those chemical 20 moieties recited above which may be substituted with one or more of the following: -F, -Cl, -Br, -I, -NO<sub>2</sub>, -CN, straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> monofluoroalkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> polyfluoroalkyl, straight chained or 25 branched C<sub>2</sub>-C<sub>7</sub> alkenyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkynyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>3</sub>-C<sub>7</sub> monofluorocycloalkyl, C<sub>3</sub>-C<sub>7</sub> polyfluorocycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, -N(R<sub>4</sub>)<sub>2</sub>, -OR<sub>4</sub>, -COR<sub>4</sub>, -NCOR<sub>4</sub>, -CO<sub>2</sub>R<sub>4</sub>, -CON(R<sub>4</sub>)<sub>2</sub> or (CH<sub>2</sub>)<sub>n</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-CH<sub>3</sub>.

30 The term "heteroaryl" further includes the N-oxides of those chemical moieties recited above which include at least one nitrogen atom.

In the present invention the term "aryl" is phenyl or naphthyl. The term "aryl" also includes phenyl and naphthyl which may be substituted with one or more of the following: -F, -Cl, -Br, -I, -NO<sub>2</sub>, -CN, straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> monofluoroalkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> polyfluoroalkyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkynyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>3</sub>-C<sub>7</sub> monofluorocycloalkyl, C<sub>3</sub>-C<sub>7</sub> polyfluorocycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, -N(R<sub>4</sub>)<sub>2</sub>, -OR<sub>4</sub>, -SR<sub>4</sub>, -OCOR<sub>4</sub>, -COR<sub>4</sub>, -NCOR<sub>4</sub>, -CO<sub>2</sub>R<sub>4</sub>, -CON(R<sub>4</sub>)<sub>2</sub> or (CH<sub>2</sub>)<sub>n</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-CH<sub>3</sub>.

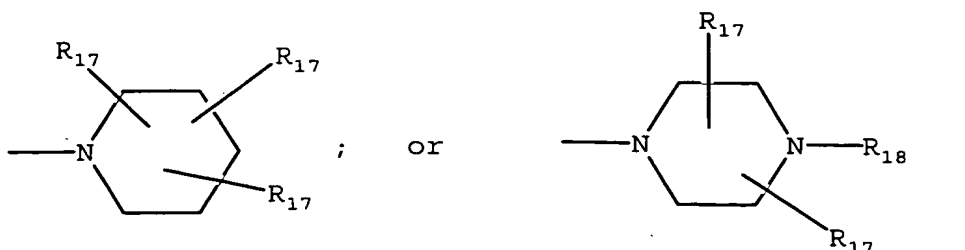
15

In one embodiment of any of the compounds described herein, the compound is enantiomerically or diasteriomERICALLY pure. In one embodiment of any of the compounds described herein, the compound is enantiomerically and diasteriomERICALLY pure.

20

In one embodiment, X is:

25

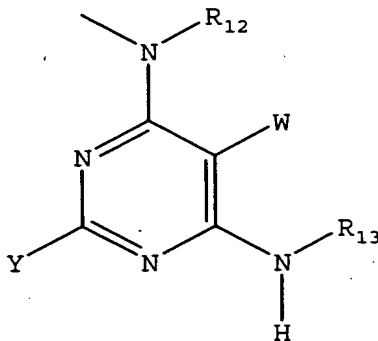




In one embodiment, X is  $\text{NR}_{11}\text{R}_{12}$  and  $\text{R}_{11}$  is H or straight chained or branched  $\text{C}_1\text{-C}_7$  alkyl.

5

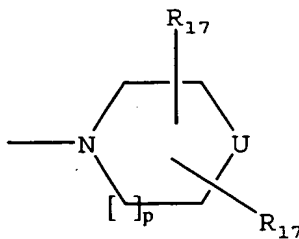
In one embodiment, the compound has the structure:



In one embodiment,  $\text{R}_{13}$  is a bicyclic alkyl ring system,  
10 cyclohexyl or aryl.

In one embodiment,  $\text{R}_{14}$  is H, straight chained or branched  $\text{C}_1\text{-C}_6$  alkyl or  $(\text{CH}_2)_q\text{-O-}(\text{CH}_2)_m\text{-CH}_3$ .

15 In one embodiment, Y is

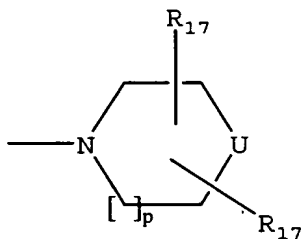


In one embodiment, U is  $\text{NR}_{16}$ .

In one embodiment,  $R_{16}$  is  $(CH_2)_m-Z$ .

In one embodiment  $Z$  is aryl or heteroaryl.

5 In one embodiment,  $Y$  is

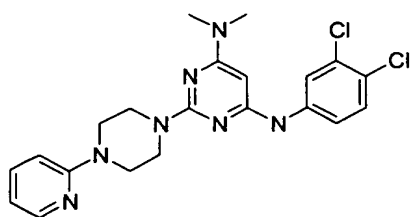
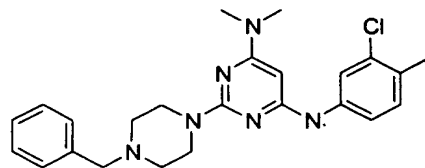
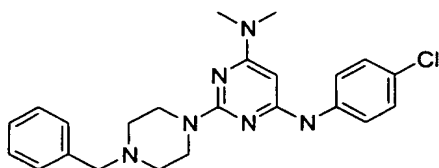
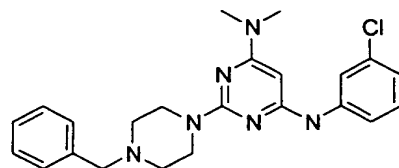
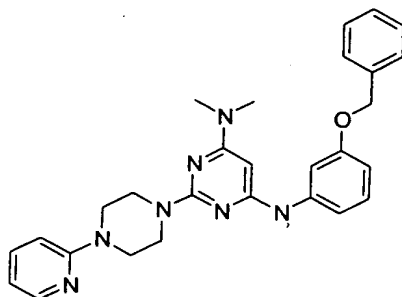
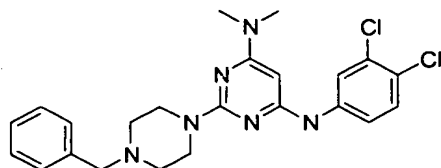
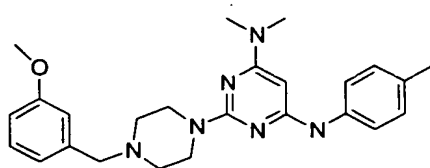


In one embodiment,  $U$  is  $NR_{16}$ .

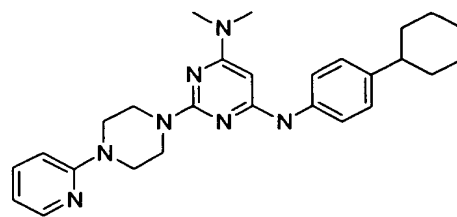
10

In one embodiment, the compound is selected from the group consisting of:

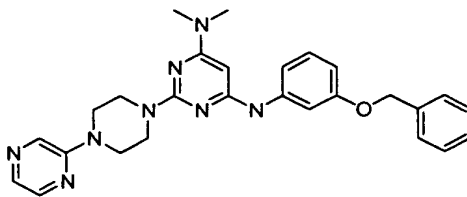
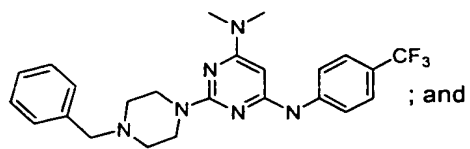
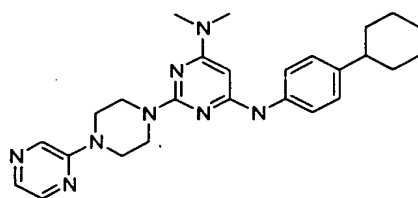
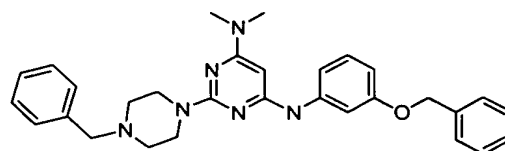
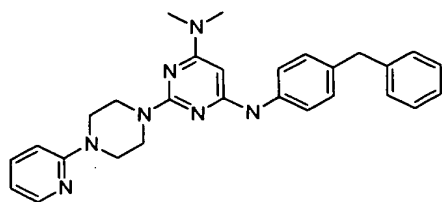
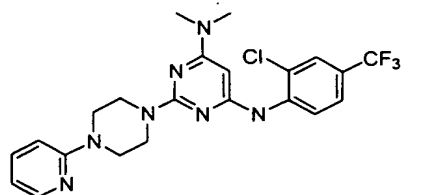
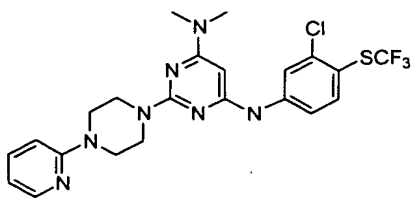
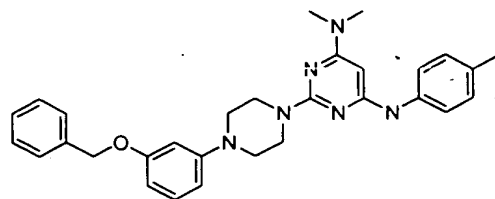
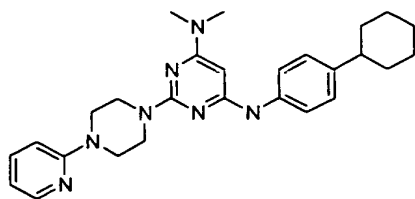
15



; and



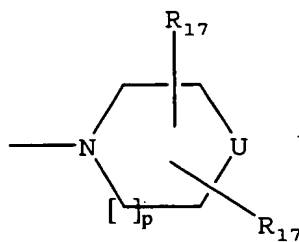
In one embodiment, the compound is selected from the group consisting of:



5

In one embodiment, X is  $\text{N}(\text{CH}_3)_2$ .

In one embodiment, Y is



5

In one embodiment, R<sub>13</sub> is an aryl substituted with a C<sub>1</sub>-C<sub>10</sub> straight chained alkyl.

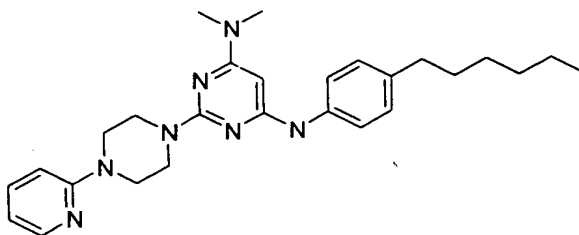
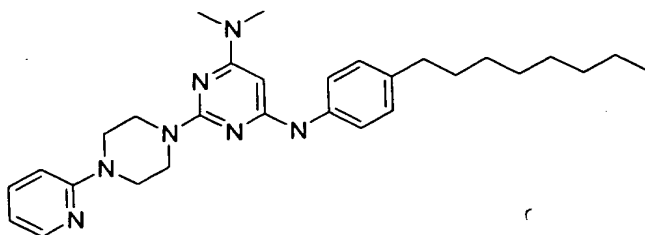
10

15

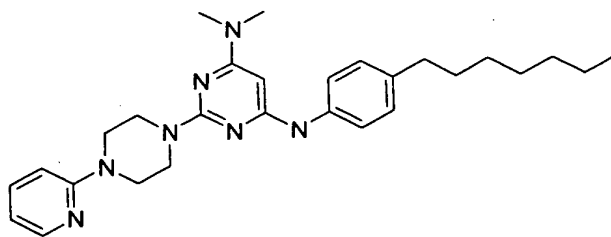
20

25

In one embodiment, the compound is selected from a group consisting of:



; and



5

The invention provides a pharmaceutical composition comprising a therapeutically effective amount of any of the compounds described herein and a pharmaceutically acceptable carrier.

The invention provides a pharmaceutical composition made by combining a therapeutically effective amount of any of the compounds described herein and a pharmaceutically acceptable carrier.

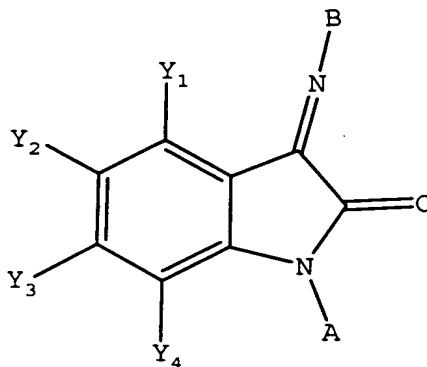
The invention provides a process for making a pharmaceutical composition comprising combining a therapeutically effective amount of any of the compounds  
5 described herein and a pharmaceutically acceptable carrier.

The invention provides a method of treating a subject suffering from depression which comprises administering  
10 to the subject an amount of any of the compounds described herein effective to treat the subject's depression.

The invention provides a method of treating a subject  
15 suffering from anxiety which comprises administering to the subject an amount of any of the compounds described herein effective to treat the subject's anxiety.

The invention provides a method of treating a subject  
20 suffering from depression and anxiety which comprises administering to the subject an amount of any of the compounds described herein effective to treat the subject's depression and anxiety.

The invention provides a method of treating a subject suffering from depression which comprises administering to the subject an amount of compound effective to treat  
 5 the subject's depression wherein the compound has the structure:



10 wherein each of  $Y_1$ ,  $Y_2$ ,  $Y_3$ , and  $Y_4$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl, or  $C_5$ - $C_7$  cycloalkenyl; -F, -Cl, -Br, or -  
 15 I; - $NO_2$ ; - $N_3$ ; -CN; - $OR_4$ , - $SR_4$ , - $OCOR_4$ , - $COR_4$ , - $NCOR_4$ , - $N(R_4)_2$ , - $CON(R_4)_2$ , or - $COOR_4$ ; aryl or heteroaryl; or any two of  $Y_1$ ,  $Y_2$ ,  $Y_3$  and  $Y_4$  present on adjacent carbon atoms can constitute a methylenedioxy group;

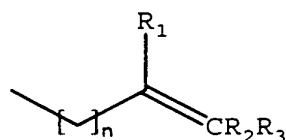
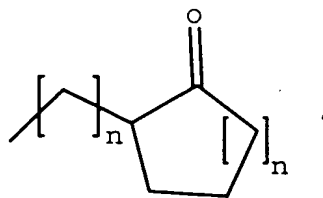
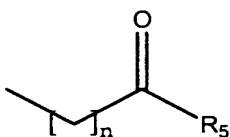
20 wherein each  $R_4$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$  cycloalkenyl, aryl or aryl( $C_1$ - $C_6$ )alkyl;



wherein A is A', Q<sub>3</sub>, Q<sub>4</sub>, Q<sub>5</sub>, straight chained or  
 branched C<sub>1</sub>-C<sub>7</sub> alkyl, aryl, heteroaryl, aryl(C<sub>1</sub>-  
 C<sub>6</sub>)alkyl, heteroaryl(C<sub>1</sub>-C<sub>6</sub>)alkyl, aryl substituted  
 5 with an aryl or heteroaryl, heteroaryl substituted  
 with an aryl or heteroaryl; or (CHR<sub>17</sub>)-(CHR<sub>17</sub>)<sub>n</sub>-Z;

wherein A' is

10

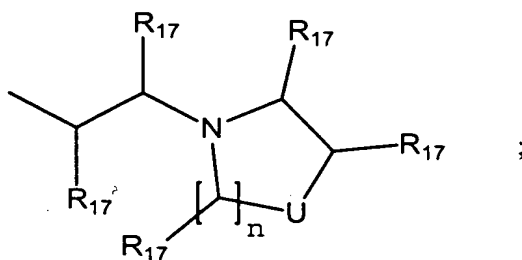


; or



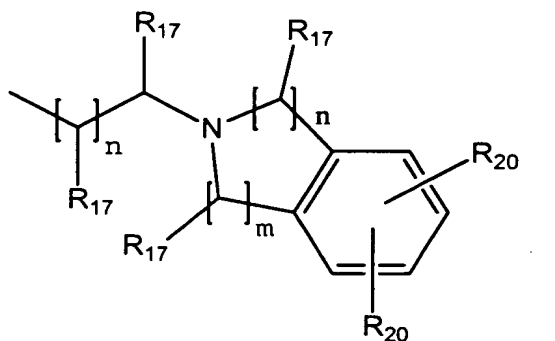
wherein Q<sub>3</sub> is

15



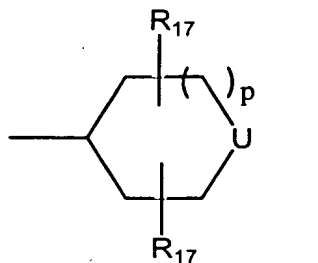
20

wherein Q<sub>4</sub> is



5

wherein Q<sub>5</sub> is



wherein R<sub>1</sub> and R<sub>2</sub> are each independently H, straight  
10 chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, -F, -Cl, -Br, -I, -  
NO<sub>2</sub>, or -CN;

wherein R<sub>3</sub> is H, straight chained or branched C<sub>1</sub>-C<sub>7</sub>  
15 alkyl, -F, -Cl, -Br, -I, -NO<sub>2</sub>, -CN, -OR<sub>6</sub>, aryl or  
heteroaryl;

wherein R<sub>5</sub> is straight chained or branched C<sub>1</sub>-C<sub>7</sub>  
alkyl, -N(R<sub>4</sub>)<sub>2</sub>, -OR<sub>6</sub> or aryl;

20 wherein R<sub>6</sub> is straight chained or branched C<sub>1</sub>-C<sub>7</sub>  
alkyl or aryl;

wherein each  $R_{17}$  is independently H; straight chained or branched  $C_1$ - $C_7$  alkyl, straight chained or branched  $C_1$ - $C_7$  monofluoroalkyl, straight chained or branched  $C_1$ - $C_7$  polyfluoroalkyl, straight chained or branched  $C_2$ - $C_7$  alkenyl, straight chained or branched  $C_2$ - $C_7$  alkynyl,  $C_5$ - $C_7$  cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_n-O-(CH_2)_m-CH_3$ ;

wherein each  $R_{20}$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl or  $C_5$ - $C_7$  cycloalkenyl; -F, -Cl, -Br, or -I;  $-NO_2$ ;  $-N_3$ ; -CN; -OR<sub>21</sub>, -OCOR<sub>21</sub>, -COR<sub>21</sub>, -NCOR<sub>21</sub>,  $-N(R_{21})_2$ ,  $-CON(R_{21})_2$ , or -COOR<sub>21</sub>; aryl or heteroaryl; or two  $R_{20}$  groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each  $R_{21}$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$  cycloalkenyl, aryl or aryl( $C_1$ - $C_6$ )alkyl;

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

wherein each p is an integer from 0 to 2 inclusive;

wherein U is O,  $-NR_{16}$ , S,  $C(R_{17})_2$ , or  $-NSO_2R_{16}$ ;

wherein Z is C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>4</sub>-C<sub>7</sub> cyclic ether, C<sub>4</sub>-C<sub>7</sub> cyclic thioether, aryl, or heteroaryl;

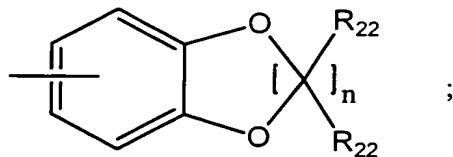
5 wherein R<sub>16</sub> is straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> monofluoroalkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> polyfluoroalkyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkynyl,  
10 C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, -(CH<sub>2</sub>)<sub>m</sub>-Z, or (CH<sub>2</sub>)<sub>q</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-CH<sub>3</sub>;

wherein q is an integer from 2 to 4 inclusive;

15 wherein B is aryl, heteroaryl, aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl, tricyclic heteroaryl or Q<sub>6</sub>; provided however, if B is aryl or heteroaryl the carbon atom or carbon atoms ortho to the nitrogen atom of the imine bond may only be substituted with  
20 one or more of the following -F, -Cl, -Br, -I, -CN, methyl, ethyl or methoxy;

25 wherein a tricyclic heteroaryl is a fused three member aromatic system in which one or more of the rings is heteroaryl; carbazole; or acridine;

wherein Q<sub>6</sub> is

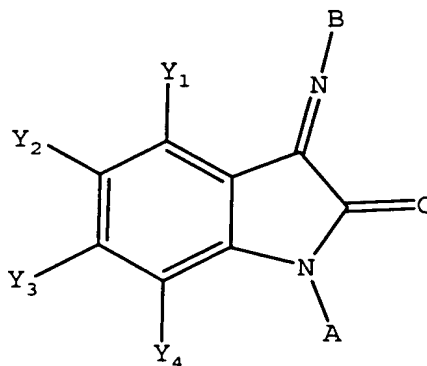


30

wherein each  $R_{22}$  is independently H, F, Cl, or straight chained or branched  $C_1-C_4$  alkyl;

5 or a pharmaceutically acceptable salt thereof.

The invention provides a method of treating a subject suffering from depression which comprises administering to the subject an amount of compound effective to treat  
10 the subject's depression wherein the compound has the structure:

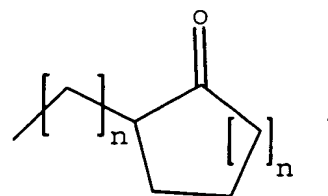
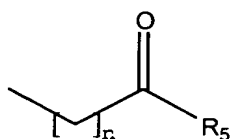


wherein each of  $Y_1$ ,  $Y_2$ ,  $Y_3$ , and  $Y_4$  is independently -  
15 H; straight chained or branched  $C_1-C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2-C_7$  alkenyl or alkynyl;  $C_3-C_7$  cycloalkyl, or  $C_5-C_7$  cycloalkenyl; -F, -Cl, -Br, or -I; - $NO_2$ ; - $N_3$ ; -CN; - $OR_4$ , - $SR_4$ , - $OCOR_4$ , - $COR_4$ , - $NCOR_4$ , -  
20  $N(R_4)_2$ , - $CON(R_4)_2$ , or - $COOR_4$ ; aryl or heteroaryl; or any two of  $Y_1$ ,  $Y_2$ ,  $Y_3$  and  $Y_4$  present on adjacent carbon atoms can constitute a methylenedioxy group;

wherein each  $R_4$  is independently -H; straight chained  
25 or branched  $C_1-C_7$  alkyl, monofluoroalkyl or

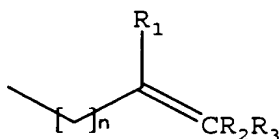
polyfluoroalkyl; straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl or alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, aryl or aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl;

5 wherein A is A', straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, aryl, heteroaryl, aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl or heteroaryl(C<sub>1</sub>-C<sub>6</sub>)alkyl;

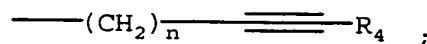


wherein A' is

10



; or



15

wherein R<sub>1</sub> and R<sub>2</sub> are each independently H, straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, -F, -Cl, -Br, -I, -NO<sub>2</sub>, or -CN;

20

wherein R<sub>3</sub> is H, straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, -F, -Cl, -Br, -I, -NO<sub>2</sub>, -CN, -OR<sub>6</sub> aryl or heteroaryl;

wherein R<sub>5</sub> is straight chained or branched C<sub>1</sub>-C<sub>7</sub>

alkyl,  $-N(R_4)_2$ ,  $-OR_6$  or aryl;

wherein  $R_6$  is straight chained or branched  $C_1-C_7$  alkyl or aryl;

5

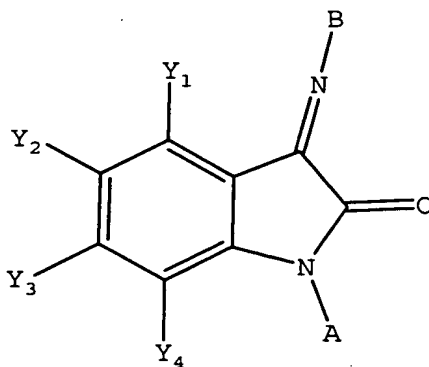
wherein B is aryl, or heteroaryl; provided however, if B is aryl or heteroaryl the carbon atom or carbon atoms ortho to the nitrogen atom of the imine bond may only be substituted with one or more of the  
10 following  $-F$ ,  $-Cl$ ,  $-Br$ ,  $-I$ ,  $-CN$ , methyl, ethyl or methoxy;

wherein n is an integer from 1 to 4 inclusive;

15

or a pharmaceutically acceptable salt thereof.

The invention provides a method of treating a subject suffering from depression which comprises administering to the subject an amount of compound effective to treat  
20 the subject's depression wherein the compound has the structure:



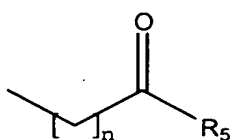
wherein each of  $Y_1$ ,  $Y_2$ ,  $Y_3$ , and  $Y_4$  is independently -  
25 H; straight chained or branched  $C_1-C_7$  alkyl,

monofluoroalkyl or polyfluoroalkyl; straight chained  
 or branched C<sub>2</sub>-C<sub>7</sub> alkenyl or alkynyl; C<sub>3</sub>-C<sub>7</sub>  
 cycloalkyl, or C<sub>5</sub>-C<sub>7</sub> cycloalkenyl; -F, -Cl, -Br, or -  
 I; -NO<sub>2</sub>; -N<sub>3</sub>; -CN; -OR<sub>4</sub>, -SR<sub>4</sub>, -OCOR<sub>4</sub>, -COR<sub>4</sub>, -NCOR<sub>4</sub>, -  
 5 N(R<sub>4</sub>)<sub>2</sub>, -CON(R<sub>4</sub>)<sub>2</sub>, or -COOR<sub>4</sub>; aryl or heteroaryl; or  
 any two of Y<sub>1</sub>, Y<sub>2</sub>, Y<sub>3</sub> and Y<sub>4</sub> present on adjacent  
 carbon atoms can constitute a methylenedioxy group;

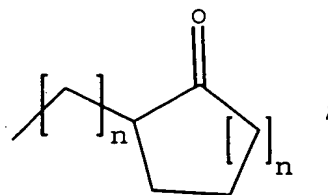
wherein each R<sub>4</sub> is independently -H; straight chained  
 10 or branched C<sub>1</sub>-C<sub>7</sub> alkyl, monofluoroalkyl or  
 polyfluoroalkyl; straight chained or branched C<sub>2</sub>-C<sub>7</sub>  
 alkenyl or alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>5</sub>-C<sub>7</sub>  
 cycloalkenyl, aryl or aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl;

15 wherein A is A', straight chained or branched C<sub>1</sub>-C<sub>7</sub>  
 alkyl, aryl, heteroaryl, aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl or  
 heteroaryl(C<sub>1</sub>-C<sub>6</sub>)alkyl;

wherein A' is

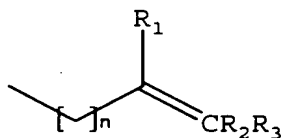


;

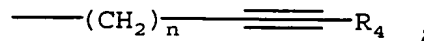


;

20



; or



;

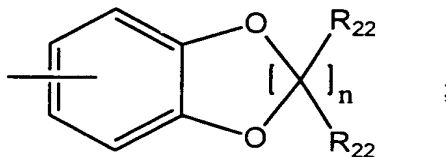


wherein B is aryl substituted with an aryl or  
heteroaryl, heteroaryl substituted with an aryl or  
5 heteroaryl, tricyclic heteroaryl or Q<sub>6</sub>;

wherein a tricyclic heteroaryl is a fused three ring  
aromatic system in which one or more of the rings is  
heteroaryl; carbazole; or acridine;

10

wherein Q<sub>6</sub> is



wherein n is an integer from 1 to 4 inclusive;

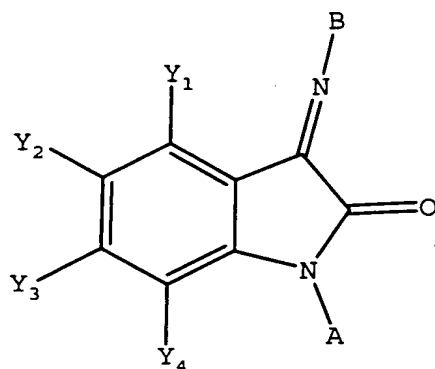
15

wherein each R<sub>22</sub> is independently H, F,  
Cl, or straight chained or branched C<sub>1</sub>-C<sub>4</sub> alkyl;

or a pharmaceutically acceptable salt thereof.

20

The invention provides a method of treating a subject  
suffering from depression which comprises administering  
25 to the subject an amount of compound effective to treat  
the subject's depression wherein the compound has the  
structure:

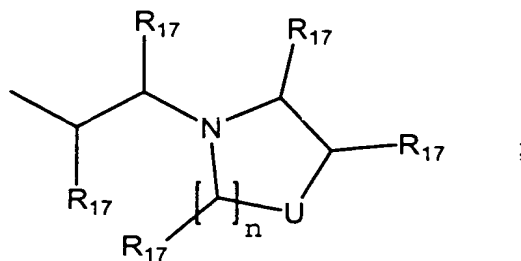


wherein each of  $Y_1$ ,  $Y_2$ ,  $Y_3$ , and  $Y_4$  is independently -  
 H; straight chained or branched  $C_1$ - $C_7$  alkyl,  
 5. monofluoroalkyl or polyfluoroalkyl; straight chained  
 or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$   
 cycloalkyl, or  $C_5$ - $C_7$  cycloalkenyl; -F, -Cl, -Br, or -  
 I; - $NO_2$ ; - $N_3$ ; -CN; - $OR_4$ , - $SR_4$ , - $OCOR_4$ , - $COR_4$ , - $NCOR_4$ , -  
 $N(R_4)_2$ , - $CON(R_4)_2$ , or - $COOR_4$ ; aryl or heteroaryl; or  
 10 any two of  $Y_1$ ,  $Y_2$ ,  $Y_3$  and  $Y_4$  present on adjacent  
 carbon atoms can constitute a methylenedioxy group;

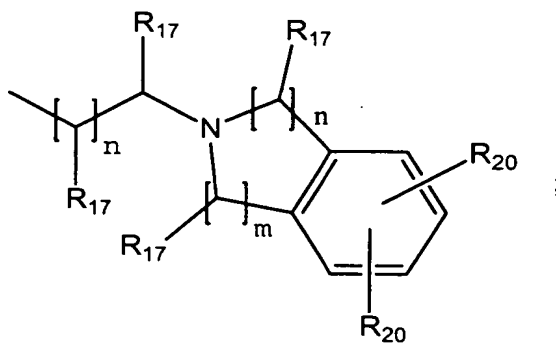
wherein each  $R_4$  is independently -H; straight chained  
 or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or  
 15 polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$   
 alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$   
 cycloalkenyl, aryl or aryl( $C_1$ - $C_6$ )alkyl;

wherein A is  $Q_3$ ,  $Q_4$ ,  $Q_5$ , aryl substituted with an  
 20 aryl or heteroaryl, heteroaryl substituted with an  
 aryl or heteroaryl, or  $(CHR_{17}) - (CHR_{17})_n - Z$ ;

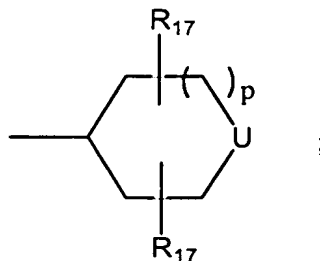
wherein  $Q_3$  is



wherein Q<sub>4</sub> is



5 wherein Q<sub>5</sub> is



10 wherein each R<sub>17</sub> is independently H; straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> monofluoroalkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> polyfluoroalkyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkynyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, -(CH<sub>2</sub>)<sub>m</sub>-Z, or (CH<sub>2</sub>)<sub>n</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-CH<sub>3</sub>;  
15

wherein each  $R_{20}$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl or  $C_5$ - $C_7$  cycloalkenyl; -F, -Cl, -Br, or -I; - $NO_2$ ; - $N_3$ ; -CN; -  
 5  $OR_{21}$ , - $OCOR_{21}$ , - $COR_{21}$ , - $NCOR_{21}$ , - $N(R_{21})_2$ , - $CON(R_{21})_2$ , or - $COOR_{21}$ ; aryl or heteroaryl; or two  $R_{20}$  groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

10

wherein each  $R_{21}$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$  cycloalkenyl or aryl;  
 15

wherein each  $R_{22}$  is independently H, F, Cl, or straight chained or branched  $C_1$ - $C_4$  alkyl;

20

wherein  $q$  is an integer from 2 to 4 inclusive;

wherein each  $m$  is an integer from 0 to 4 inclusive;

wherein each  $n$  is an integer from 1 to 4 inclusive;

25

wherein each  $p$  is an integer from 0 to 2 inclusive;

wherein  $U$  is O, - $NR_{16}$ , S,  $C(R_{17})_2$ , or - $NSO_2R_{16}$ ;

30

wherein  $Z$  is  $C_3$ - $C_{10}$  cycloalkyl,  $C_4$ - $C_7$  cyclic ether,  $C_4$ - $C_7$  cyclic thioether, aryl, or heteroaryl;

wherein  $R_{16}$  is straight chained or branched  $C_1$ - $C_7$  alkyl, straight chained or branched  $C_1$ - $C_7$  monofluoroalkyl, straight chained or branched  $C_1$ - $C_7$  polyfluoroalkyl, straight chained or branched  $C_2$ - $C_7$  alkenyl, straight chained or branched  $C_2$ - $C_7$  alkynyl,  $C_5$ - $C_7$  cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_q-O-(CH_2)_m-CH_3$ ;

wherein B is aryl, or heteroaryl; provided however, if B is aryl or heteroaryl the carbon atom or carbon atoms ortho to the nitrogen atom of the imine bond may only be substituted with one or more of the following -F, -Cl, -Br, -I, -CN, methyl, ethyl or methoxy;

or a pharmaceutically acceptable salt thereof.

As used in the present invention, the term "cycloalkyl" includes  $C_3$ - $C_7$  cycloalkyl moieties which may be substituted with one or more of the following: -F,  $-NO_2$ , -CN, straight chained or branched  $C_1$ - $C_7$  alkyl, straight chained or branched  $C_1$ - $C_7$  monofluoroalkyl, straight chained or branched  $C_1$ - $C_7$  polyfluoroalkyl, straight chained or branched  $C_2$ - $C_7$  alkenyl, straight chained or branched  $C_2$ - $C_7$  alkynyl,  $C_3$ - $C_7$  cycloalkyl,  $C_3$ - $C_7$  monofluorocycloalkyl,  $C_3$ - $C_7$  polyfluorocycloalkyl,  $C_5$ - $C_7$  cycloalkenyl,  $-N(R_4)_2$ ,  $-OR_4$ ,  $-COR_4$ ,  $-NCOR_4$ ,  $-CO_2R_4$ ,  $-CON(R_4)_2$  or  $(CH_2)_n-O-(CH_2)_m-CH_3$ .

As used in the present invention, the term "cycloalkenyl" includes  $C_5$ - $C_7$  cycloalkenyl moieties which may be substituted with one or more of the

following: -F, -Cl, -Br, -I, -NO<sub>2</sub>, -CN, straight  
 chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, straight chained or  
 branched C<sub>1</sub>-C<sub>7</sub> monofluoroalkyl, straight chained or  
 branched C<sub>1</sub>-C<sub>7</sub> polyfluoroalkyl, straight chained or  
 branched C<sub>2</sub>-C<sub>7</sub> alkenyl, straight chained or branched  
 C<sub>2</sub>-C<sub>7</sub> alkynyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>3</sub>-C<sub>7</sub>  
 monofluorocycloalkyl, C<sub>3</sub>-C<sub>7</sub> polyfluorocycloalkyl, C<sub>5</sub>-  
 C<sub>7</sub> cycloalkenyl, -N(R<sub>4</sub>)<sub>2</sub>, -OR<sub>4</sub>, -COR<sub>4</sub>, -NCOR<sub>4</sub>,  
 -CO<sub>2</sub>R<sub>4</sub>, -CON(R<sub>4</sub>)<sub>2</sub> or (CH<sub>2</sub>)<sub>n</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-CH<sub>3</sub>.

In the present invention, the term "heteroaryl" is  
 used to include five and six membered unsaturated  
 rings that may contain one or more oxygen, sulfur,  
 or nitrogen atoms. Examples of heteroaryl groups  
 include, but are not limited to, furanyl, thienyl,  
 pyrrolyl, oxazolyl, thiazolyl, imidazolyl,  
 pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl,  
 triazolyl, thiadiazolyl, pyridyl, pyridazinyl,  
 pyrimidinyl, pyrazinyl, and triazinyl.

In addition the term "heteroaryl" is used to include  
 fused bicyclic ring systems that may contain one or  
 more heteroatoms such as oxygen, sulfur and  
 nitrogen. Examples of such heteroaryl groups  
 include, but are not limited to, indoliziny, indolyl,  
 isoindolyl, benzo[b]furanyl, benzo[b]thiophenyl,  
 indazolyl, benzimidazolyl, purinyl, benzoxazolyl,  
 benzisoxazolyl, benzo[b]thiazolyl, imidazo[2,1-b]thiazolyl,  
 cinnolinyl, quinazolinyl, quinoxalinyl, 1,8-  
 naphthyridinyl, pteridinyl, quinolinyl, isoquinolinyl,  
 phthalimidyl and 2,1,3-

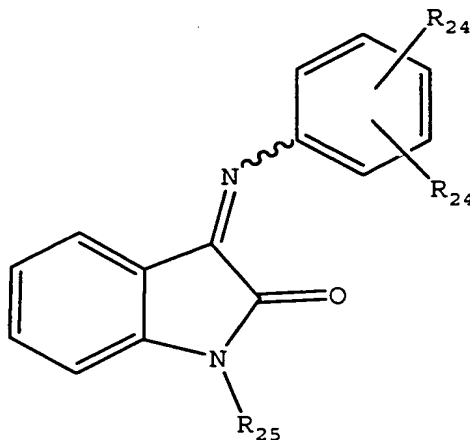
benzothiazolyl.

The term "heteroaryl" also includes those chemical moieties recited above which may be substituted with one or more of the following: -F, -Cl, -Br, -I, -NO<sub>2</sub>, -CN, straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> monofluoroalkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> polyfluoroalkyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkynyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>3</sub>-C<sub>7</sub> monofluorocycloalkyl, C<sub>3</sub>-C<sub>7</sub> polyfluorocycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, -N(R<sub>4</sub>)<sub>2</sub>, -OR<sub>4</sub>, -COR<sub>4</sub>, -NCOR<sub>4</sub>, -CO<sub>2</sub>R<sub>4</sub>, -CON(R<sub>4</sub>)<sub>2</sub> or (CH<sub>2</sub>)<sub>n</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-CH<sub>3</sub>.

The term "heteroaryl" further includes the N-oxides of those chemical moieties recited above which include at least one nitrogen atom.

In the present invention the term "aryl" is phenyl or naphthyl. The term "aryl" also includes phenyl and naphthyl which may be substituted with one or more of the following: -F, -Cl, -Br, -I, -NO<sub>2</sub>, -CN, straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> monofluoroalkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> polyfluoroalkyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkynyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>3</sub>-C<sub>7</sub> monofluorocycloalkyl, C<sub>3</sub>-C<sub>7</sub> polyfluorocycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, -N(R<sub>4</sub>)<sub>2</sub>, -OR<sub>4</sub>, -SR<sub>4</sub>, -OCOR<sub>4</sub>, -COR<sub>4</sub>, -NCOR<sub>4</sub>, -CO<sub>2</sub>R<sub>4</sub>, -CON(R<sub>4</sub>)<sub>2</sub> or (CH<sub>2</sub>)<sub>n</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-CH<sub>3</sub>.

The present invention also provides a method of treating a subject suffering from depression which compromises administering to the subject an amount  
 5 of compound effective to treat the subject's depression, wherein the compound has the structure:



10 wherein each  $R_{24}$  is independently one or more of the following: H, F, Cl, Br, I,  $CF_3$ ,  $OCH_3$  or  $NO_2$ ;

wherein  $R_{25}$  is methyl, ethyl, allyl, phenyl and the phenyl is optionally substituted with a F, Cl, Br,  
 15  $CF_3$ ,  $NO_2$ .

In one embodiment of any one of the methods described herein, the compound is enantiomerically or  
 20 diastereomerically pure. In one embodiment of any of the methods described herein, the compound is enantiomerically and diastereomerically pure.

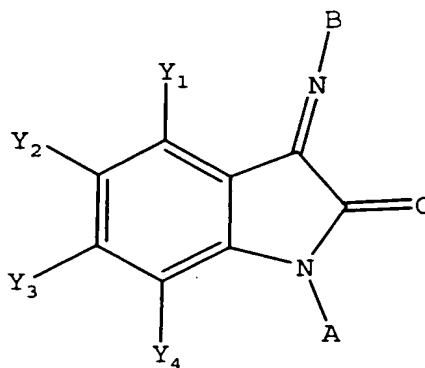
In one embodiment, the compound is a pure Z imine isomer



or a pure Z alkene isomer. In one embodiment, the compound is a pure E imine isomer or a pure E alkene isomer.

- 5 In one embodiment, the compound is administered orally.

In one embodiment, the compound has the structure:



10

wherein each of  $Y_1$ ,  $Y_2$ ,  $Y_3$ , and  $Y_4$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl,  $-CF_3$ , -F, -Cl, -Br, -I,  $-OR_4$ ,  $-N(R_4)_2$ , or  $-CON(R_4)_2$ ;

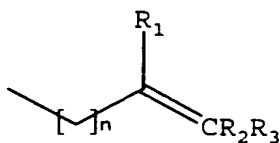
15

wherein each  $R_4$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl,  $-CF_3$ , or phenyl;

20

wherein A is  $A'$ , straight chained or branched  $C_1$ - $C_7$  alkyl, aryl, heteroaryl, aryl( $C_1$ - $C_6$ )alkyl or heteroaryl( $C_1$ - $C_6$ )alkyl; and

wherein  $A'$  is



In one embodiment, B is heteroaryl. In one embodiment, B is aryl.

5

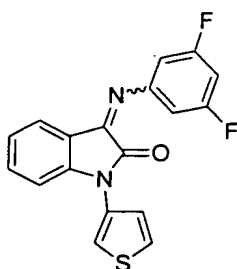
In one embodiment, B is phenyl and the phenyl is optionally substituted with one or more of the following: -F, -Cl, -Br, -CF<sub>3</sub>, straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, -N(R<sub>4</sub>)<sub>2</sub>, -OR<sub>4</sub>, -COR<sub>4</sub>, -NCOR<sub>4</sub>, -CO<sub>2</sub>R<sub>4</sub>, or -CON(R<sub>4</sub>)<sub>2</sub>.

10

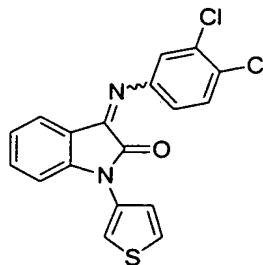
In one embodiment, A is aryl. In one embodiment, A is heteroaryl.

In one embodiment, the compound is selected from the group consisting of:

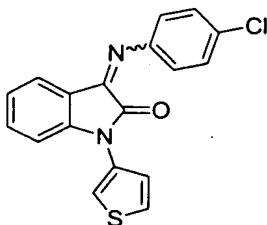
15



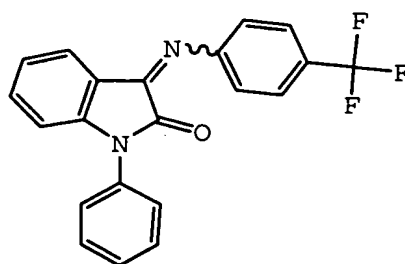
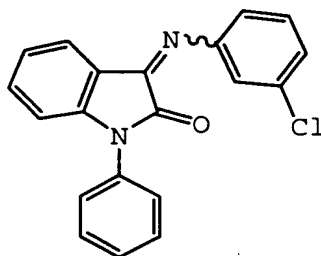
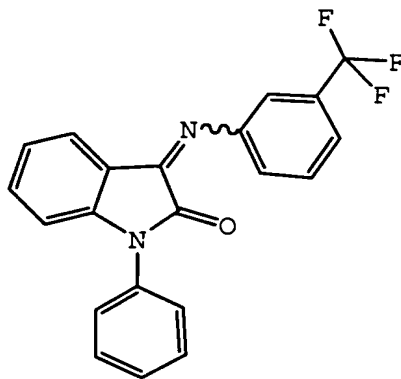
;

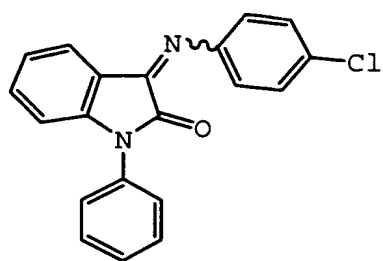


; and

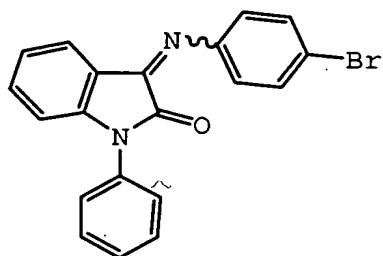


In one embodiment, the compound is selected from the  
5 group consisting of:

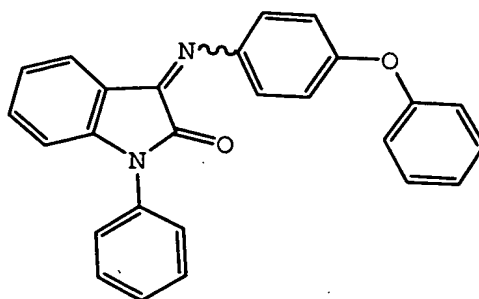




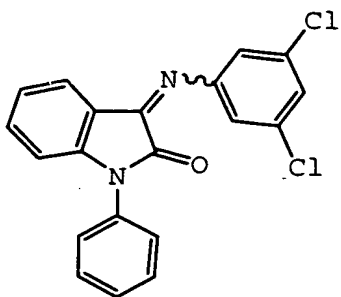
;



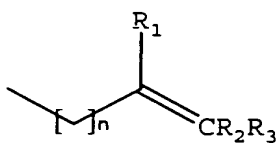
;



; and



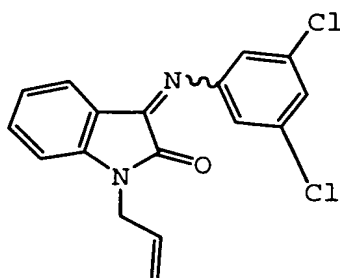
In one embodiment, A is A' and A' is



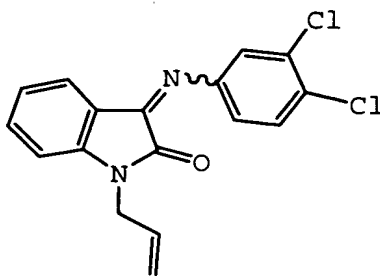
5

In one embodiment, the compound is:

10



; or

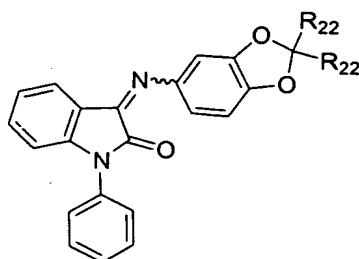


In one embodiment, B is Q<sub>6</sub>.

5 In one embodiment, A is aryl.

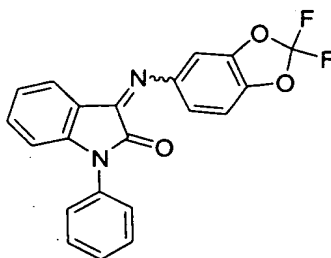
In one embodiment, the compound has the structure:

10



15

In one embodiment, the compound is:



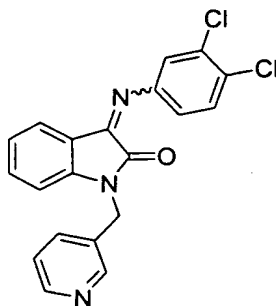
20

In one embodiment, B is aryl.

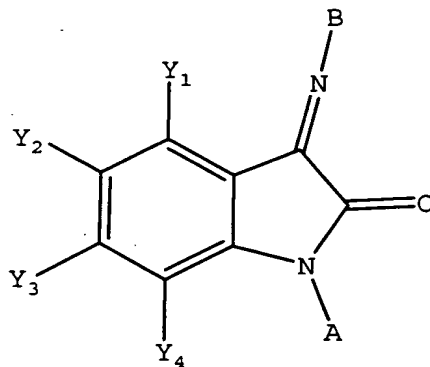
In one embodiment, A is  $(\text{CHR}_{17}) - (\text{CHR}_{17})_n - \text{Z}$ .

In one embodiment, the compound is:

5



- 10 The invention provides a method of treating a subject suffering from anxiety which comprises administering to the subject an amount of compound effective to treat the subject's anxiety wherein the compound has the structure:



15

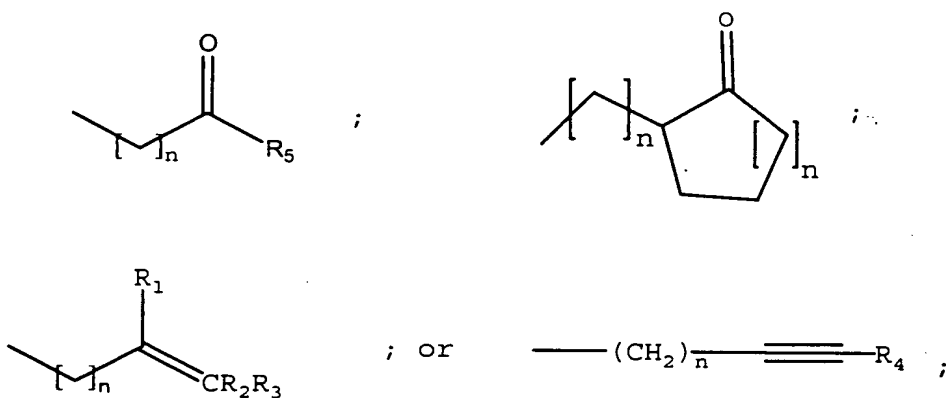
wherein each of  $Y_1$ ,  $Y_2$ ,  $Y_3$ , and  $Y_4$  is independently -

H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl, or  $C_5$ - $C_7$  cycloalkenyl; -F, -Cl, -Br, or -I; - $NO_2$ ; - $N_3$ ; -CN; - $OR_4$ , - $SR_4$ , - $OCOR_4$ , - $COR_4$ , - $NCOR_4$ , - $N(R_4)_2$ , - $CON(R_4)_2$ , or - $COOR_4$ ; aryl or heteroaryl; or any two of  $Y_1$ ,  $Y_2$ ,  $Y_3$  and  $Y_4$  present on adjacent carbon atoms can constitute a methylenedioxy group;

wherein each  $R_4$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$  cycloalkenyl, aryl or aryl( $C_1$ - $C_6$ )alkyl;

wherein A is  $A'$ ,  $Q_3$ ,  $Q_4$ ,  $Q_5$ , straight chained or branched  $C_1$ - $C_7$  alkyl, aryl, heteroaryl, aryl( $C_1$ - $C_6$ )alkyl, heteroaryl( $C_1$ - $C_6$ )alkyl, aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl; or  $(CHR_{17})-(CHR_{17})_n$ ;

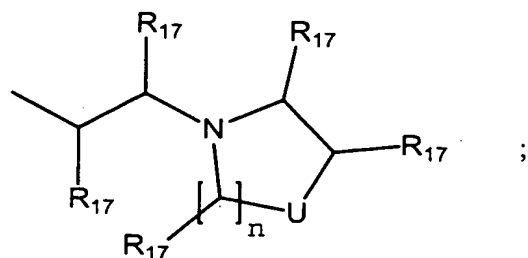
wherein  $A'$  is





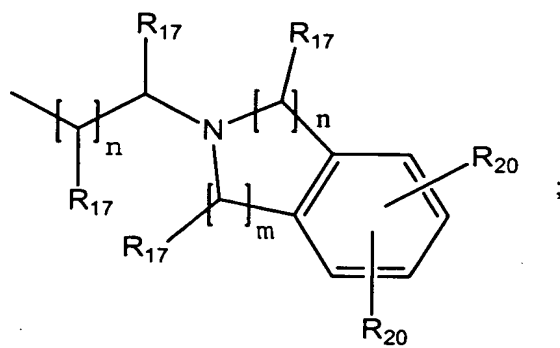
wherein  $Q_3$  is

5



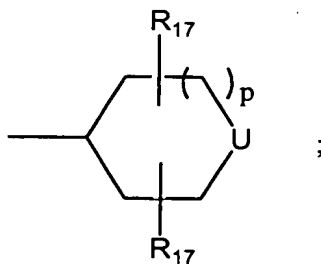
10

wherein  $Q_4$  is



15

wherein  $Q_5$  is



wherein  $R_1$  and  $R_2$  are each independently H, straight chained or branched  $C_1$ - $C_7$  alkyl, -F, -Cl, -Br, -I, - $NO_2$ , or -CN;

5

wherein  $R_3$  is H, straight chained or branched  $C_1$ - $C_7$  alkyl, -F, -Cl, -Br, -I, - $NO_2$ , -CN, -OR<sub>6</sub>, aryl or heteroaryl;

10

wherein  $R_5$  is straight chained or branched  $C_1$ - $C_7$  alkyl, -N( $R_4$ )<sub>2</sub>, -OR<sub>6</sub> or aryl;

wherein  $R_6$  is straight chained or branched  $C_1$ - $C_7$  alkyl or aryl;

15

wherein each  $R_{17}$  is independently H; straight chained or branched  $C_1$ - $C_7$  alkyl, straight chained or branched  $C_1$ - $C_7$  monofluoroalkyl, straight chained or branched  $C_1$ - $C_7$  polyfluoroalkyl, straight chained or branched  $C_2$ - $C_7$  alkenyl, straight chained or branched  $C_2$ - $C_7$  alkynyl,  $C_5$ - $C_7$  cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_n-O-(CH_2)_m-CH_3$ ;

20

wherein each  $R_{20}$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl or  $C_5$ - $C_7$  cycloalkenyl; -F, -Cl, -Br, or -I; - $NO_2$ ; -N<sub>3</sub>; -CN; -OR<sub>21</sub>, -OCOR<sub>21</sub>, -COR<sub>21</sub>, -NCOR<sub>21</sub>, -N( $R_{21}$ )<sub>2</sub>, -CON( $R_{21}$ )<sub>2</sub>, or -COOR<sub>21</sub>; aryl or heteroaryl; or two  $R_{20}$  groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

25

30

wherein each  $R_{21}$  is independently -H; straight  
 chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or  
 polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$   
 5 alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$   
 cycloalkenyl, aryl or aryl( $C_1$ - $C_6$ )alkyl;

wherein each m is an integer from 0 to 4 inclusive;

10 wherein each n is an integer from 1 to 4 inclusive;

wherein each p is an integer from 0 to 2 inclusive;

wherein U is O,  $-NR_{16}$ , S,  $C(R_{17})_2$ , or  $-NSO_2R_{16}$ ;

15 wherein Z is  $C_3$ - $C_{10}$  cycloalkyl,  $C_4$ - $C_7$  cyclic ether,  
 $C_4$ - $C_7$  cyclic thioether, aryl, or heteroaryl;

wherein  $R_{16}$  is straight chained or branched  $C_1$ - $C_7$   
 20 alkyl, straight chained or branched  $C_1$ - $C_7$   
 monofluoroalkyl, straight chained or branched  $C_1$ - $C_7$   
 polyfluoroalkyl, straight chained or branched  $C_2$ - $C_7$   
 alkenyl, straight chained or branched  $C_2$ - $C_7$  alkynyl,  
 $C_5$ - $C_7$  cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_q-O-(CH_2)_m-CH_3$ ;

25 wherein q is an integer from 2 to 4 inclusive;

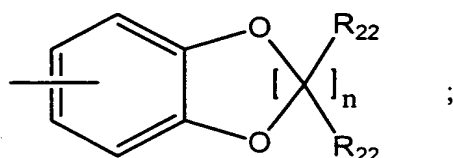
wherein B is aryl, heteroaryl, aryl substituted with  
 an aryl or heteroaryl, heteroaryl substituted with  
 30 an aryl or heteroaryl, tricyclic heteroaryl or  $Q_6$ ;  
 provided however, if B is aryl or heteroaryl the  
 carbon atom or carbon atoms ortho to the nitrogen

atom of the imine bond may only be substituted with one or more of the following -F, -Cl, -Br, -I, -CN, methyl, ethyl or methoxy;

5 wherein a tricyclic heteroaryl is a fused three member aromatic system in which one or more of the rings is heteroaryl; carbazole; or acridine;

wherein Q<sub>6</sub> is

10

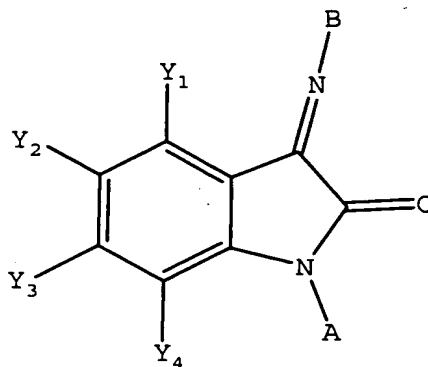


wherein each R<sub>22</sub> is independently H, F, Cl, or straight chained or branched C<sub>1</sub>-C<sub>4</sub> alkyl;

15

or a pharmaceutically acceptable salt thereof.

The invention provides a method of treating a subject suffering from anxiety which comprises administering to  
20 the subject an amount of compound effective to treat the subject's anxiety wherein the compound has the structure:

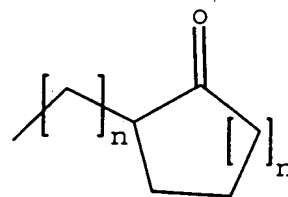
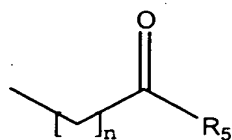


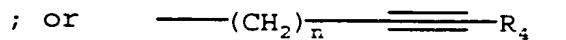
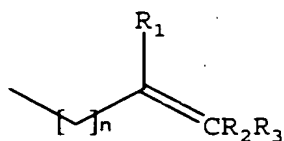
wherein each of  $Y_1$ ,  $Y_2$ ,  $Y_3$ , and  $Y_4$  is independently -  
 H; straight chained or branched  $C_1$ - $C_7$  alkyl,  
 monofluoroalkyl or polyfluoroalkyl; straight chained  
 5 or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$   
 cycloalkyl, or  $C_5$ - $C_7$  cycloalkenyl; -F, -Cl, -Br, or -  
 I; - $NO_2$ ; - $N_3$ ; -CN; - $OR_4$ , - $SR_4$ , - $OCOR_4$ , - $COR_4$ , - $NCOR_4$ , -  
 $N(R_4)_2$ , - $CON(R_4)_2$ , or - $COOR_4$ ; aryl or heteroaryl; or  
 10 any two of  $Y_1$ ,  $Y_2$ ,  $Y_3$  and  $Y_4$  present on adjacent  
 carbon atoms can constitute a methylenedioxy group;

wherein each  $R_4$  is independently -H; straight chained  
 or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or  
 polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$   
 15 alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$   
 cycloalkenyl, aryl or aryl( $C_1$ - $C_6$ )alkyl;

wherein A is A', straight chained or branched  $C_1$ - $C_7$   
 alkyl, aryl, heteroaryl, aryl( $C_1$ - $C_6$ )alkyl or  
 20 heteroaryl( $C_1$ - $C_6$ )alkyl;

wherein A' is





wherein  $\text{R}_1$  and  $\text{R}_2$  are each independently H, straight  
chained or branched  $\text{C}_1\text{-C}_7$  alkyl, -F, -Cl, -Br, -I, -  
5  $\text{NO}_2$ , or -CN;

wherein  $\text{R}_3$  is H, straight chained or branched  $\text{C}_1\text{-C}_7$   
alkyl, -F, -Cl, -Br, -I, - $\text{NO}_2$ , -CN, - $\text{OR}_6$  aryl or  
heteroaryl;

10 wherein  $\text{R}_5$  is straight chained or branched  $\text{C}_1\text{-C}_7$   
alkyl, - $\text{N}(\text{R}_4)_2$ , - $\text{OR}_6$  or aryl;

wherein  $\text{R}_6$  is straight chained or branched  $\text{C}_1\text{-C}_7$   
15 alkyl or aryl;

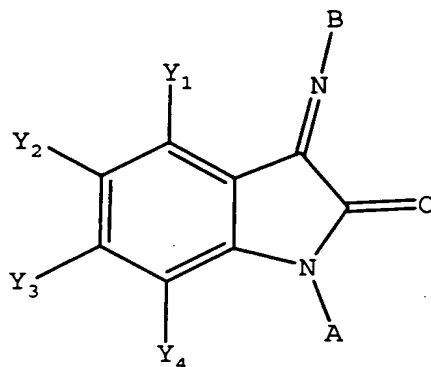
wherein B is aryl, or heteroaryl; provided however,  
if B is aryl or heteroaryl the carbon atom or carbon  
atoms ortho to the nitrogen atom of the imine bond  
20 may only be substituted with one or more of the  
following -F, -Cl, -Br, -I, -CN, methyl, ethyl or  
methoxy;

wherein n is an integer from 1 to 4 inclusive;

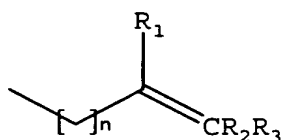
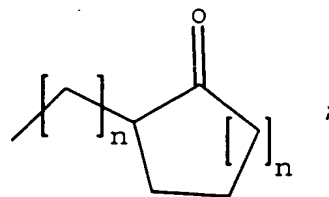
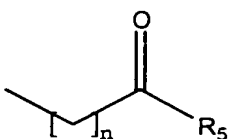
25 or a pharmaceutically acceptable salt thereof.

The invention provides a method of treating a subject  
suffering from anxiety which comprises administering to

the subject an amount of compound effective to treat the subject's anxiety wherein the compound has the structure:



5. wherein each of  $Y_1$ ,  $Y_2$ ,  $Y_3$ , and  $Y_4$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl, or  $C_5$ - $C_7$  cycloalkenyl; -F, -Cl, -Br, or -I; - $NO_2$ ; - $N_3$ ; -CN; - $OR_4$ , - $SR_4$ , - $OCOR_4$ , - $COR_4$ , - $NCOR_4$ , - $N(R_4)_2$ , - $CON(R_4)_2$ , or - $COOR_4$ ; aryl or heteroaryl; or any two of  $Y_1$ ,  $Y_2$ ,  $Y_3$  and  $Y_4$  present on adjacent carbon atoms can constitute a methylenedioxy group;
- 10
- 15 wherein each  $R_4$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$  cycloalkenyl, aryl or aryl( $C_1$ - $C_6$ )alkyl;
- 20
- wherein A is A', straight chained or branched  $C_1$ - $C_7$  alkyl, aryl, heteroaryl, aryl( $C_1$ - $C_6$ )alkyl or heteroaryl( $C_1$ - $C_6$ )alkyl;
- 25
- wherein A' is



; or



5

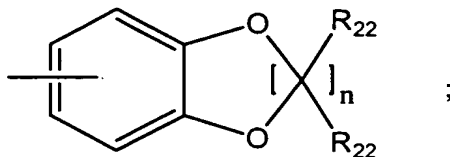
wherein B is aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl, tricyclic heteroaryl or Q<sub>6</sub>;

10

wherein a tricyclic heteroaryl is a fused three ring aromatic system in which one or more of the rings is heteroaryl; carbazole; or acridine;

15

wherein Q<sub>6</sub> is



wherein n is an integer from 1 to 4 inclusive;

20

wherein each R<sub>22</sub> is independently H, F, Cl, or straight chained or branched C<sub>1</sub>-C<sub>4</sub> alkyl;

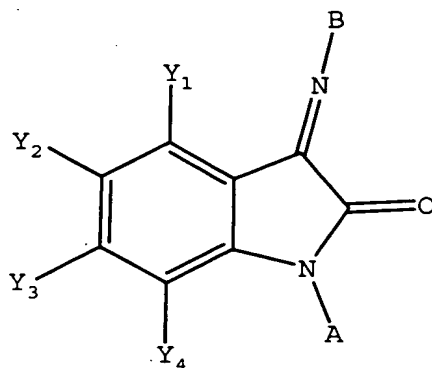


or a pharmaceutically acceptable salt thereof.

5

The invention provides a method of treating a subject suffering from anxiety which comprises administering to the subject an amount of compound effective to treat the subject's anxiety wherein the compound has the structure:

10



15

wherein each of  $Y_1$ ,  $Y_2$ ,  $Y_3$ , and  $Y_4$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl, or  $C_5$ - $C_7$  cycloalkenyl; -F, -Cl, -Br, or -I; - $NO_2$ ; - $N_3$ ; -CN; - $OR_4$ , - $SR_4$ , - $OCOR_4$ , - $COR_4$ , - $NCOR_4$ , - $N(R_4)_2$ , - $CON(R_4)_2$ , or - $COOR_4$ ; aryl or heteroaryl; or any two of  $Y_1$ ,  $Y_2$ ,  $Y_3$  and  $Y_4$  present on adjacent carbon atoms can constitute a methylenedioxy group;

20

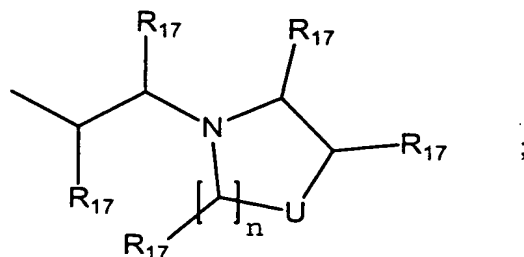
25

wherein each  $R_4$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$  cycloalkenyl, aryl or aryl( $C_1$ - $C_6$ )alkyl;

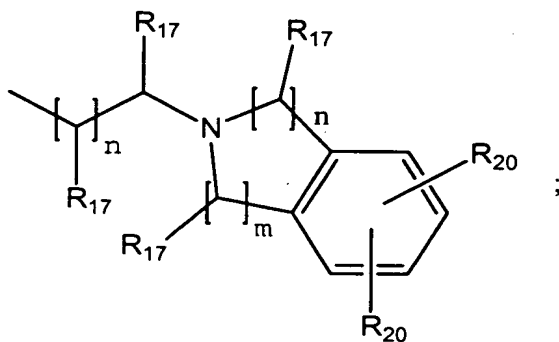
wherein A is Q<sub>3</sub>, Q<sub>4</sub>, Q<sub>5</sub>, aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl, or (CHR<sub>17</sub>)<sub>n</sub>-Z;

5

wherein Q<sub>3</sub> is

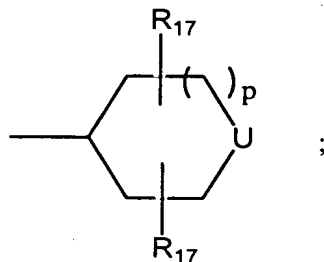


wherein Q<sub>4</sub> is



10

wherein Q<sub>5</sub> is



15

wherein each R<sub>17</sub> is independently H; straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> monofluoroalkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> polyfluoroalkyl, straight chained or branched

$C_2-C_7$  alkenyl, straight chained or branched  $C_2-C_7$  alkynyl,  $C_5-C_7$  cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_n-O-(CH_2)_m-CH_3$ ;

5

wherein each  $R_{20}$  is independently -H; straight chained or branched  $C_1-C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2-C_7$  alkenyl or alkynyl;  $C_3-C_7$  cycloalkyl or  $C_5-C_7$  cycloalkenyl; -F, -Cl, -Br, or -I; -NO<sub>2</sub>; -N<sub>3</sub>; -CN; -OR<sub>21</sub>, -OCOR<sub>21</sub>, -COR<sub>21</sub>, -NCOR<sub>21</sub>, -N(R<sub>21</sub>)<sub>2</sub>, -CON(R<sub>21</sub>)<sub>2</sub>, or -COOR<sub>21</sub>; aryl or heteroaryl; or two  $R_{20}$  groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

15

wherein each  $R_{21}$  is independently -H; straight chained or branched  $C_1-C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2-C_7$  alkenyl or alkynyl;  $C_3-C_7$  cycloalkyl,  $C_5-C_7$  cycloalkenyl or aryl;

20

wherein each  $R_{22}$  is independently H, F, Cl, or straight chained or branched  $C_1-C_4$  alkyl;

25

wherein  $q$  is an integer from 2 to 4 inclusive;

wherein each  $m$  is an integer from 0 to 4 inclusive;

wherein each  $n$  is an integer from 1 to 4 inclusive;

30

wherein each  $p$  is an integer from 0 to 2 inclusive;

wherein U is O,  $-NR_{16}$ , S,  $C(R_{17})_2$ , or  $-NSO_2R_{16}$ ;

wherein Z is  $C_3-C_{10}$  cycloalkyl,  $C_4-C_7$  cyclic ether,  $C_4-C_7$  cyclic thioether, aryl, or heteroaryl;

5

wherein  $R_{16}$  is straight chained or branched  $C_1-C_7$  alkyl, straight chained or branched  $C_1-C_7$  monofluoroalkyl, straight chained or branched  $C_1-C_7$  polyfluoroalkyl, straight chained or branched  $C_2-C_7$  alkenyl, straight chained or branched  $C_2-C_7$  alkynyl,  $C_5-C_7$  cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_q-O-(CH_2)_m-CH_3$ ;

10

wherein B is aryl, or heteroaryl; provided however, if B is aryl or heteroaryl the carbon atom or carbon atoms ortho to the nitrogen atom of the imine bond may only be substituted with one or more of the following -F, -Cl, -Br, -I, -CN, methyl, ethyl or methoxy;

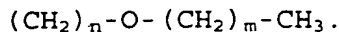
15

or a pharmaceutically acceptable salt thereof.

20

As used in the present invention, the term "cycloalkyl" includes  $C_3-C_7$  cycloalkyl moieties which may be substituted with one or more of the following: -F,  $-NO_2$ , -CN, straight chained or branched  $C_1-C_7$  alkyl, straight chained or branched  $C_1-C_7$  monofluoroalkyl, straight chained or branched  $C_1-C_7$  polyfluoroalkyl, straight chained or branched  $C_2-C_7$  alkenyl, straight chained or branched  $C_2-C_7$  alkynyl,  $C_3-C_7$  cycloalkyl,  $C_3-C_7$  monofluorocycloalkyl,  $C_3-C_7$  polyfluorocycloalkyl,  $C_5-C_7$  cycloalkenyl,  $-N(R_4)_2$ ,  $-OR_4$ ,  $-COR_4$ ,  $-NCOR_4$ ,  $-CO_2R_4$ ,  $-CON(R_4)_2$  or

30



As used in the present invention, the term "cycloalkenyl" includes C<sub>5</sub>-C<sub>7</sub> cycloalkenyl moieties which may be substituted with one or more of the following: -F, -Cl, -Br, -I, -NO<sub>2</sub>, -CN, straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> monofluoroalkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> polyfluoroalkyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkynyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>3</sub>-C<sub>7</sub> monofluorocycloalkyl, C<sub>3</sub>-C<sub>7</sub> polyfluorocycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, -N(R<sub>4</sub>)<sub>2</sub>, -OR<sub>4</sub>, -COR<sub>4</sub>, -NCOR<sub>4</sub>, -CO<sub>2</sub>R<sub>4</sub>, -CON(R<sub>4</sub>)<sub>2</sub> or (CH<sub>2</sub>)<sub>n</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-CH<sub>3</sub>.

In the present invention, the term "heteroaryl" is used to include five and six membered unsaturated rings that may contain one or more oxygen, sulfur, or nitrogen atoms. Examples of heteroaryl groups include, but are not limited to, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, and triazinyl.

In addition the term "heteroaryl" is used to include fused bicyclic ring systems that may contain one or more heteroatoms such as oxygen, sulfur and nitrogen. Examples of such heteroaryl groups include, but are not limited to, indoliziny, indolyl, isoindolyl, benzo[b]furanyl, benzo[b]thiophenyl, indazolyl, benzimidazolyl,

purinyl, benzoxazolyl, benzisoxazolyl,  
 benzo[b]thiazolyl, imidazo[2,1-b]thiazolyl,  
 cinnolinyl, quinazolinyl, quinoxalinyl, 1,8-  
 naphthyridinyl, pteridinyl, quinolinyl,  
 5 isoquinolinyl, phthalimidyl and 2,1,3-  
 benzothiazolyl.

The term "heteroaryl" also includes those chemical  
 moieties recited above which may be substituted with  
 10 one or more of the following: -F, -Cl, -Br, -I, -  
 NO<sub>2</sub>, -CN, straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl,  
 straight chained or branched C<sub>1</sub>-C<sub>7</sub> monofluoroalkyl,  
 straight chained or branched C<sub>1</sub>-C<sub>7</sub> polyfluoroalkyl,  
 straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl, straight  
 15 chained or branched C<sub>2</sub>-C<sub>7</sub> alkynyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl,  
 C<sub>3</sub>-C<sub>7</sub> monofluorocycloalkyl, C<sub>3</sub>-C<sub>7</sub>  
 polyfluorocycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, -N(R<sub>4</sub>)<sub>2</sub>, -  
 OR<sub>4</sub>, -COR<sub>4</sub>, -NCOR<sub>4</sub>, -CO<sub>2</sub>R<sub>4</sub>, -CON(R<sub>4</sub>)<sub>2</sub> or (CH<sub>2</sub>)<sub>n</sub>-O-  
 (CH<sub>2</sub>)<sub>m</sub>-CH<sub>3</sub>.

20 The term "heteroaryl" further includes the N-oxides  
 of those chemical moieties recited above which  
 include at least one nitrogen atom.

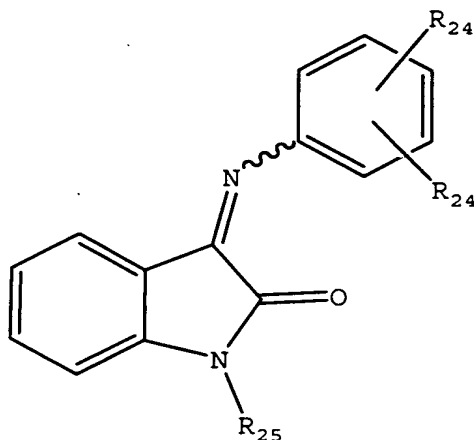
25 In the present invention the term "aryl" is phenyl  
 or naphthyl. The term "aryl" also includes phenyl  
 and naphthyl which may be substituted with one or  
 more of the following: -F, -Cl, -Br, -I, -NO<sub>2</sub>, -CN,  
 straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, straight  
 30 chained or branched C<sub>1</sub>-C<sub>7</sub> monofluoroalkyl, straight  
 chained or branched C<sub>1</sub>-C<sub>7</sub> polyfluoroalkyl, straight  
 chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl, straight chained

or branched C<sub>2</sub>-C<sub>7</sub> alkynyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>3</sub>-C<sub>7</sub> monofluorocycloalkyl, C<sub>3</sub>-C<sub>7</sub> polyfluorocycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, -N(R<sub>4</sub>)<sub>2</sub>, -OR<sub>4</sub>, -SR<sub>4</sub>, -OCOR<sub>4</sub>, -COR<sub>4</sub>, -NCOR<sub>4</sub>, -CO<sub>2</sub>R<sub>4</sub>, -CON(R<sub>4</sub>)<sub>2</sub> or (CH<sub>2</sub>)<sub>n</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-CH<sub>3</sub>.

5

The present invention also provides a method of treating a subject suffering from anxiety which compromises administering to the subject an amount of compound effective to treat the subject's anxiety where in the compound has the structure:

10



15

wherein each R<sub>24</sub> is independently one or more of the following: H, F, Cl, Br, I, CF<sub>3</sub>, OCH<sub>3</sub> or NO<sub>2</sub>;

wherein R<sub>25</sub> is methyl, ethyl, allyl, phenyl and the phenyl is optionally substituted with a F, Cl, Br, CF<sub>3</sub>, NO<sub>2</sub>.

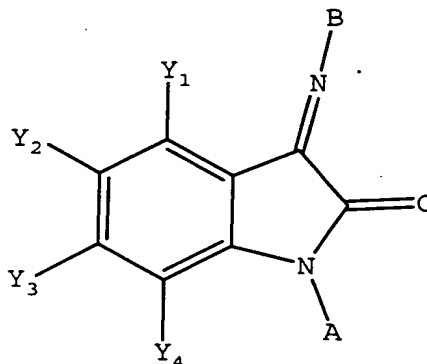
20

In one embodiment of any of the methods described herein, the compound is enantiomerically and diastereomerically pure. In one embodiment of any of the methods described herein, the compound is enantiomerically or

diastereomerically pure.

In one embodiment of any of the methods described herein,  
the compound is a pure Z imine isomer or a pure Z alkene  
isomer. In one embodiment, the compound is a pure E  
imine isomer or a pure E alkene isomer.

In one embodiment, the compound has the structure:



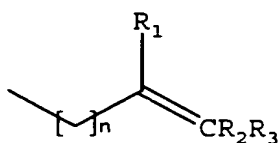
wherein each of  $Y_1$ ,  $Y_2$ ,  $Y_3$ , and  $Y_4$  is independently -  
H; straight chained or branched  $C_1$ - $C_7$  alkyl,  $-CF_3$ , -  
F,  $-Cl$ ,  $-Br$ ,  $-I$ ,  $-OR_4$ ,  $-N(R_4)_2$ , or  $-CON(R_4)_2$ ;

wherein each  $R_4$  is independently -H; straight chained  
or branched  $C_1$ - $C_7$  alkyl,  $-CF_3$ , or phenyl;

wherein A is  $A'$ , straight chained or branched  $C_1$ - $C_7$   
alkyl, aryl, heteroaryl, aryl( $C_1$ - $C_6$ )alkyl or  
heteroaryl( $C_1$ - $C_6$ )alkyl; and

wherein  $A'$  is





In one embodiment, B is heteroaryl. In one embodiment, B is aryl.

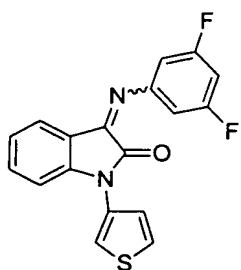
5

In one embodiment, B is phenyl and the phenyl is optionally substituted with one or more of the following: -F, -Cl, -Br, -CF<sub>3</sub>, straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, -N(R<sub>4</sub>)<sub>2</sub>, -OR<sub>4</sub>, -COR<sub>4</sub>, -NCOR<sub>4</sub>, -CO<sub>2</sub>R<sub>4</sub>, or -CON(R<sub>4</sub>)<sub>2</sub>.

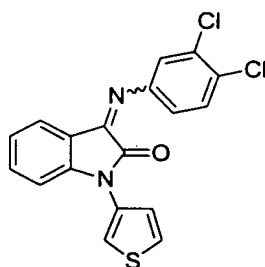
10

In one embodiment, A is aryl. In one embodiment, A is heteroaryl.

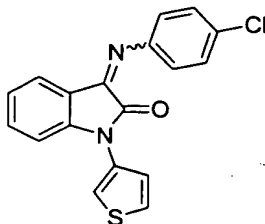
In one embodiment, the compound is selected from the group consisting of:



;

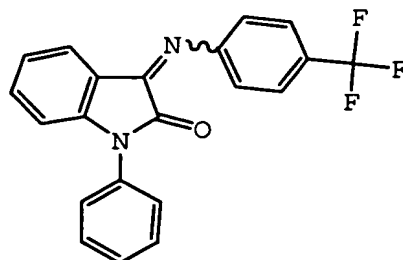
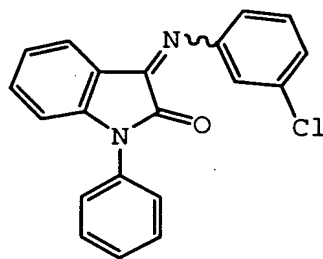
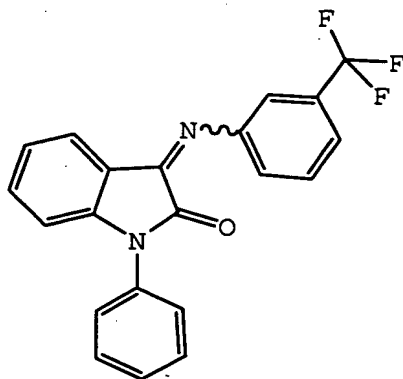


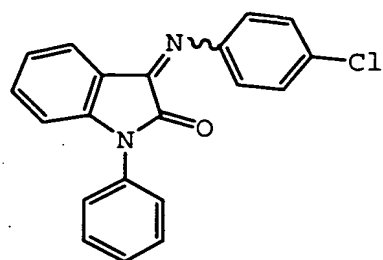
; and



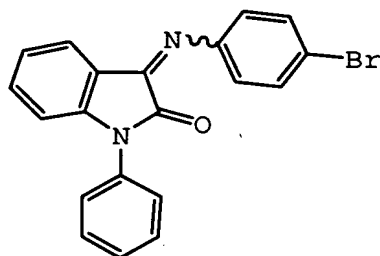
5

In one embodiment, the compound is selected from the group consisting of:

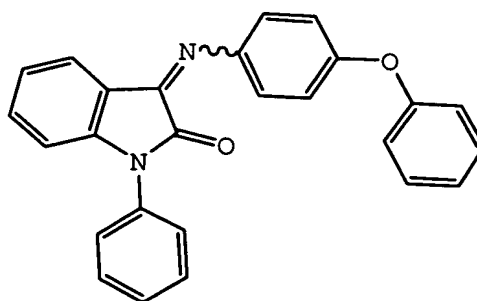




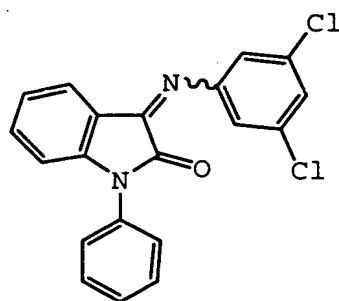
;



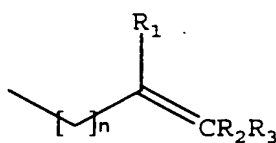
;



; and



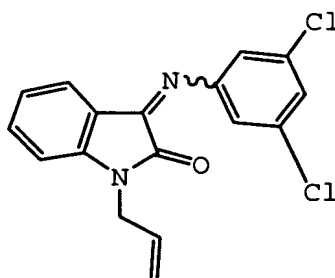
In one embodiment, A is A' and A' is



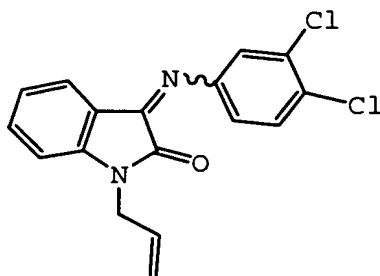
5

In one embodiment, the compound is:

10



; or

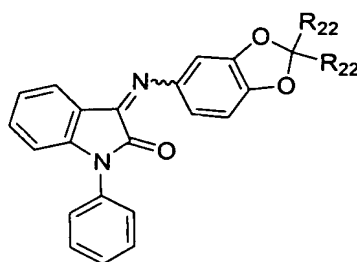


In one embodiment, B is Q<sub>6</sub>.

5 In one embodiment, A is aryl.

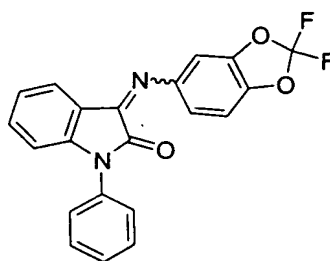
In one embodiment, the compound has the structure:

10



15

In one embodiment, the compound is:



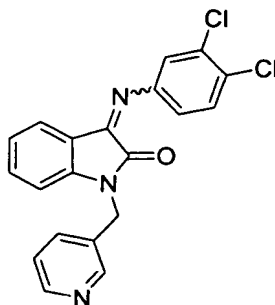
20

In one embodiment, B is aryl.

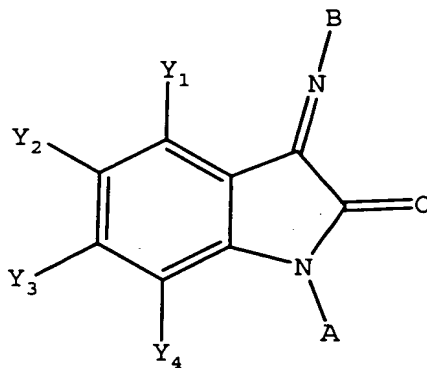
In one embodiment, A is  $(\text{CHR}_{17}) - (\text{CHR}_{17})_n - \text{Z}$ .

In one embodiment, the compound is:

5



The invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a  
10 compound having the structure:



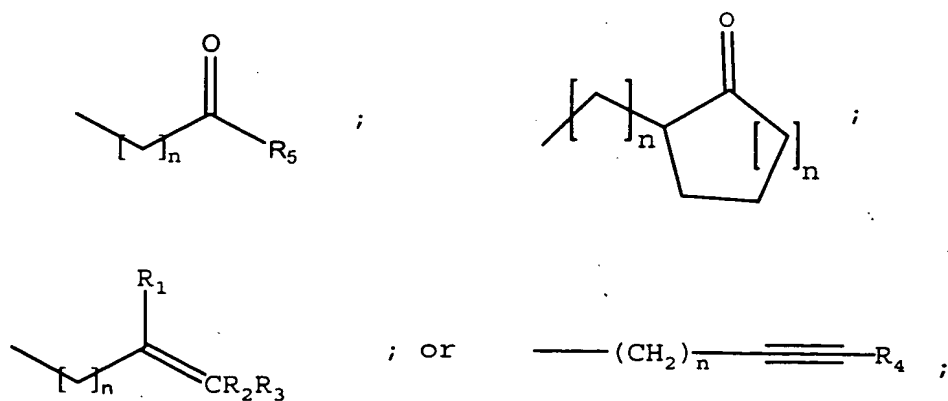
15 wherein each of  $Y_1$ ,  $Y_2$ ,  $Y_3$ , and  $Y_4$  is independently -  
H; straight chained or branched  $\text{C}_1\text{-C}_7$  alkyl,  
monofluoroalkyl or polyfluoroalkyl; straight chained

or branched C<sub>2</sub>-C<sub>7</sub> alkenyl or alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl, or C<sub>5</sub>-C<sub>7</sub> cycloalkenyl; -F, -Cl, -Br, or -I; -NO<sub>2</sub>; -N<sub>3</sub>; -CN; -OR<sub>4</sub>, -SR<sub>4</sub>, -OCOR<sub>4</sub>, -COR<sub>4</sub>, -NCOR<sub>4</sub>, -N(R<sub>4</sub>)<sub>2</sub>, -CON(R<sub>4</sub>)<sub>2</sub>, or -COOR<sub>4</sub>; aryl or heteroaryl; or  
 5 any two of Y<sub>1</sub>, Y<sub>2</sub>, Y<sub>3</sub> and Y<sub>4</sub> present on adjacent carbon atoms can constitute a methylenedioxy group;

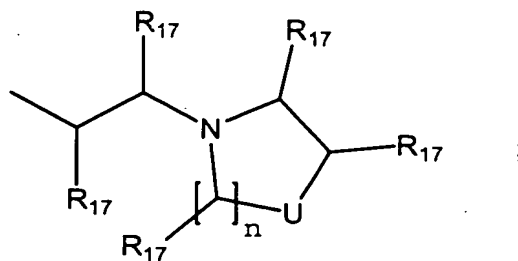
wherein each R<sub>4</sub> is independently -H; straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl or alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, aryl or aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl;  
 10

wherein A is A', Q<sub>3</sub>, Q<sub>4</sub>, Q<sub>5</sub>, straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, aryl, heteroaryl, aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl, heteroaryl(C<sub>1</sub>-C<sub>6</sub>)alkyl, aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl; or (CHR<sub>17</sub>)<sub>n</sub>-Z;  
 15

20 wherein A' is

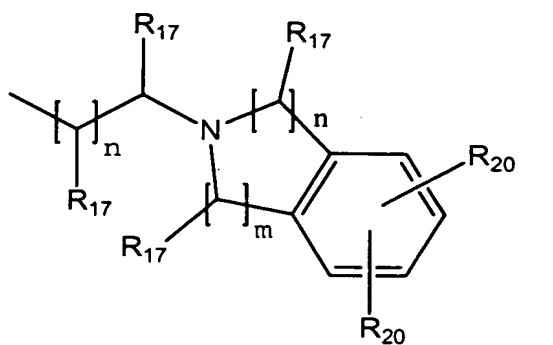


wherein  $Q_3$  is



5

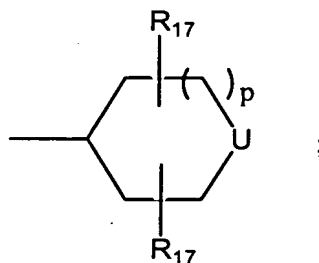
wherein  $Q_4$  is



10

15

wherein  $Q_5$  is





wherein  $R_1$  and  $R_2$  are each independently H, straight chained or branched  $C_1$ - $C_7$  alkyl, -F, -Cl, -Br, -I, - $NO_2$ , or -CN;

5

wherein  $R_3$  is H, straight chained or branched  $C_1$ - $C_7$  alkyl, -F, -Cl, -Br, -I, - $NO_2$ , -CN, -OR<sub>6</sub>, aryl or heteroaryl;

10

wherein  $R_5$  is straight chained or branched  $C_1$ - $C_7$  alkyl, -N( $R_4$ )<sub>2</sub>, -OR<sub>6</sub> or aryl;

wherein  $R_6$  is straight chained or branched  $C_1$ - $C_7$  alkyl or aryl;

15

wherein each  $R_{17}$  is independently H; straight chained or branched  $C_1$ - $C_7$  alkyl, straight chained or branched  $C_1$ - $C_7$  monofluoroalkyl, straight chained or branched  $C_1$ - $C_7$  polyfluoroalkyl, straight chained or branched  $C_2$ - $C_7$  alkenyl, straight chained or branched  $C_2$ - $C_7$  alkynyl,  $C_5$ - $C_7$  cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_n-O-(CH_2)_m-CH_3$ ;

20

wherein each  $R_{20}$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl or  $C_5$ - $C_7$  cycloalkenyl; -F, -Cl, -Br, or -I; - $NO_2$ ; -N<sub>3</sub>; -CN; -OR<sub>21</sub>, -OCOR<sub>21</sub>, -COR<sub>21</sub>, -NCOR<sub>21</sub>, -N( $R_{21}$ )<sub>2</sub>, -CON( $R_{21}$ )<sub>2</sub>, or -COOR<sub>21</sub>; aryl or heteroaryl; or two  $R_{20}$  groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

25

30

wherein each  $R_{21}$  is independently -H; straight  
 chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or  
 polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$   
 5 alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$   
 cycloalkenyl, aryl or aryl( $C_1$ - $C_6$ )alkyl;

wherein each  $m$  is an integer from 0 to 4 inclusive;

10 wherein each  $n$  is an integer from 1 to 4 inclusive;

wherein each  $p$  is an integer from 0 to 2 inclusive;

wherein  $U$  is O,  $-NR_{16}$ , S,  $C(R_{17})_2$ , or  $-NSO_2R_{16}$ ;

15

wherein  $Z$  is  $C_3$ - $C_{10}$  cycloalkyl,  $C_4$ - $C_7$  cyclic ether,  
 $C_4$ - $C_7$  cyclic thioether, aryl, or heteroaryl;

wherein  $R_{16}$  is straight chained or branched  $C_1$ - $C_7$   
 20 alkyl, straight chained or branched  $C_1$ - $C_7$   
 monofluoroalkyl, straight chained or branched  $C_1$ - $C_7$   
 polyfluoroalkyl, straight chained or branched  $C_2$ - $C_7$   
 alkenyl, straight chained or branched  $C_2$ - $C_7$  alkynyl,  
 $C_5$ - $C_7$  cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_q-O-(CH_2)_m-CH_3$ ;

25

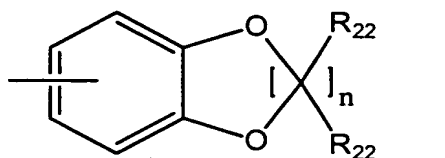
wherein  $q$  is an integer from 2 to 4 inclusive;

wherein  $B$  is aryl, heteroaryl, aryl substituted with  
 an aryl or heteroaryl, heteroaryl substituted with  
 30 an aryl or heteroaryl, tricyclic heteroaryl or  $Q_6$ ;  
 provided however, if  $B$  is aryl or heteroaryl the  
 carbon atom or carbon atoms ortho to the nitrogen

atom of the imine bond may only be substituted with one or more of the following -F, -Cl, -Br, -I, -CN, methyl, ethyl or methoxy;

- 5 wherein a tricyclic heteroaryl is a fused three member aromatic system in which one or more of the rings is heteroaryl; carbazole; or acridine;

wherein  $Q_6$  is

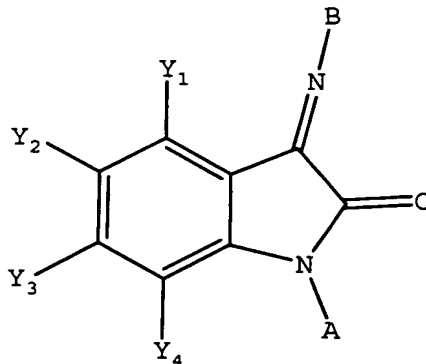


wherein each  $R_{22}$  is independently H, F, Cl, or straight chained or branched  $C_1$ - $C_4$  alkyl;

- 15 or a pharmaceutically acceptable salt thereof.

The invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound having the structure:

20

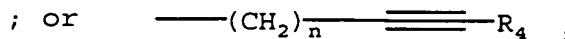
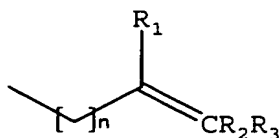
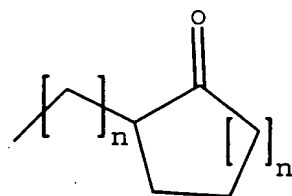
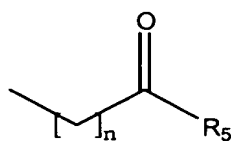


wherein each of  $Y_1$ ,  $Y_2$ ,  $Y_3$ , and  $Y_4$  is independently -  
H; straight chained or branched  $C_1$ - $C_7$  alkyl,  
monofluoroalkyl or polyfluoroalkyl; straight chained  
or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$   
5 cycloalkyl, or  $C_5$ - $C_7$  cycloalkenyl; -F, -Cl, -Br, or -  
I; -NO<sub>2</sub>; -N<sub>3</sub>; -CN; -OR<sub>4</sub>, -SR<sub>4</sub>, -OCOR<sub>4</sub>, -COR<sub>4</sub>, -NCOR<sub>4</sub>, -  
N(R<sub>4</sub>)<sub>2</sub>, -CON(R<sub>4</sub>)<sub>2</sub>, or -COOR<sub>4</sub>; aryl or heteroaryl; or  
any two of  $Y_1$ ,  $Y_2$ ,  $Y_3$  and  $Y_4$  present on adjacent  
carbon atoms can constitute a methylenedioxy group;

10 wherein each  $R_4$  is independently -H; straight chained  
or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or  
polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$   
alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$   
15 cycloalkenyl, aryl or aryl( $C_1$ - $C_6$ )alkyl;

wherein A is A', straight chained or branched  $C_1$ - $C_7$   
alkyl, aryl, heteroaryl, aryl( $C_1$ - $C_6$ )alkyl or  
heteroaryl( $C_1$ - $C_6$ )alkyl;

20 wherein A' is



wherein  $R_1$  and  $R_2$  are each independently H, straight  
5 chained or branched  $C_1$ - $C_7$  alkyl, -F, -Cl, -Br, -I, -  
NO<sub>2</sub>, or -CN;

wherein  $R_3$  is H, straight chained or branched  $C_1$ - $C_7$   
10 alkyl, -F, -Cl, -Br, -I, -NO<sub>2</sub>, -CN, -OR<sub>6</sub> aryl or  
heteroaryl;

wherein  $R_5$  is straight chained or branched  $C_1$ - $C_7$   
alkyl, -N( $R_4$ )<sub>2</sub>, -OR<sub>6</sub> or aryl;

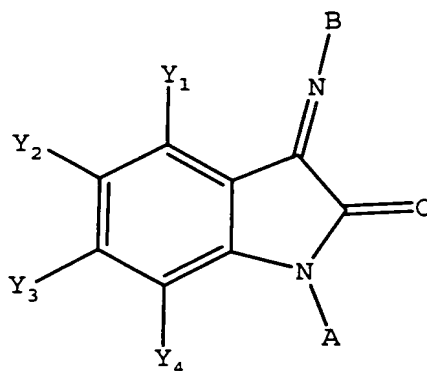
15 wherein  $R_6$  is straight chained or branched  $C_1$ - $C_7$   
alkyl or aryl;

wherein B is aryl, or heteroaryl; provided however,  
20 if B is aryl or heteroaryl the carbon atom or carbon  
atoms ortho to the nitrogen atom of the imine bond  
may only be substituted with one or more of the  
following -F, -Cl, -Br, -I, -CN, methyl, ethyl or  
methoxy;

25 wherein n is an integer from 1 to 4 inclusive;

or a pharmaceutically acceptable salt thereof.

The invention provides a pharmaceutical composition  
30 comprising a pharmaceutically acceptable carrier and a  
compound having the structure:

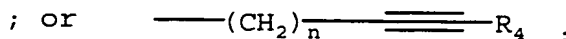
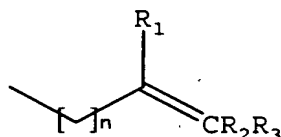
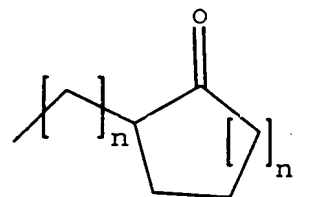
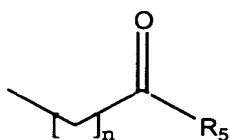


wherein each of  $Y_1$ ,  $Y_2$ ,  $Y_3$ , and  $Y_4$  is independently -  
 H; straight chained or branched  $C_1$ - $C_7$  alkyl,  
 5 monofluoroalkyl or polyfluoroalkyl; straight chained  
 or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$   
 cycloalkyl, or  $C_5$ - $C_7$  cycloalkenyl; -F, -Cl, -Br, or -  
 I; - $NO_2$ ; - $N_3$ ; -CN; - $OR_4$ , - $SR_4$ , - $OCOR_4$ , - $COR_4$ , - $NCOR_4$ , -  
 $N(R_4)_2$ , - $CON(R_4)_2$ , or - $COOR_4$ ; aryl or heteroaryl; or  
 10 any two of  $Y_1$ ,  $Y_2$ ,  $Y_3$  and  $Y_4$  present on adjacent  
 carbon atoms can constitute a methylenedioxy group;

wherein each  $R_4$  is independently -H; straight chained  
 or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or  
 15 polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$   
 alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$   
 cycloalkenyl, aryl or aryl( $C_1$ - $C_6$ )alkyl;

wherein A is A', straight chained or branched  $C_1$ - $C_7$   
 20 alkyl, aryl, heteroaryl, aryl( $C_1$ - $C_6$ )alkyl or  
 heteroaryl( $C_1$ - $C_6$ )alkyl;

wherein A' is



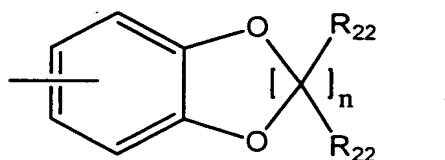
5

wherein B is aryl substituted with an aryl or  
heteroaryl, heteroaryl substituted with an aryl or  
10 heteroaryl, tricyclic heteroaryl or Q<sub>6</sub>;

wherein a tricyclic heteroaryl is a fused three ring  
aromatic system in which one or more of the rings is  
heteroaryl; carbazole; or acridine;

15

wherein Q<sub>6</sub> is



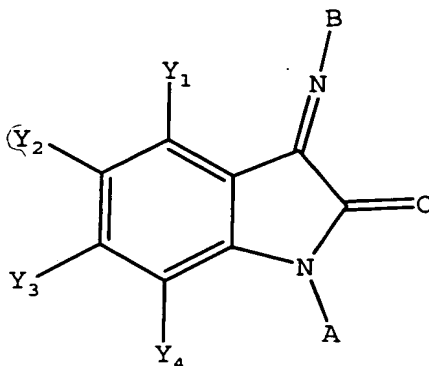
wherein n is an integer from 1 to 4 inclusive;

20

wherein each R<sub>22</sub> is independently H, F,  
Cl, or straight chained or branched C<sub>1</sub>-C<sub>4</sub> alkyl;

or a pharmaceutically acceptable salt thereof.

- 5 The invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound having the structure:



10

wherein each of  $Y_1$ ,  $Y_2$ ,  $Y_3$ , and  $Y_4$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl, or  $C_5$ - $C_7$  cycloalkenyl; -F, -Cl, -Br, or -I; - $NO_2$ ; - $N_3$ ; -CN; - $OR_4$ , - $SR_4$ , - $OCOR_4$ , - $COR_4$ , - $NCOR_4$ , - $N(R_4)_2$ , - $CON(R_4)_2$ , or - $COOR_4$ ; aryl or heteroaryl; or any two of  $Y_1$ ,  $Y_2$ ,  $Y_3$  and  $Y_4$  present on adjacent carbon atoms can constitute a methylenedioxy group;

20

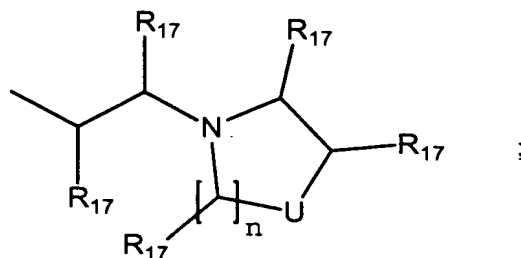
wherein each  $R_4$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$  cycloalkenyl, aryl or aryl( $C_1$ - $C_6$ )alkyl;

25



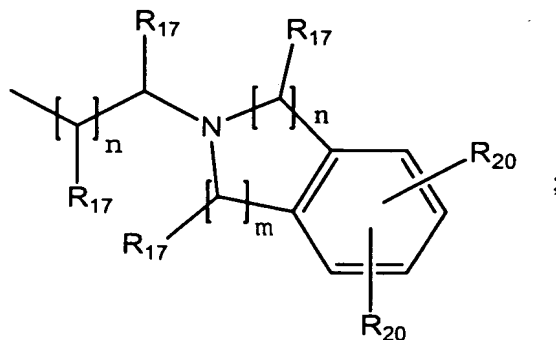
wherein A is Q<sub>3</sub>, Q<sub>4</sub>, Q<sub>5</sub>, aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl, or (CHR<sub>17</sub>) - (CHR<sub>17</sub>)<sub>n</sub>-Z;

5 wherein Q<sub>3</sub> is

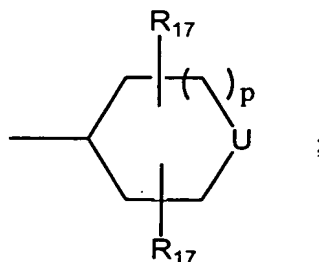


10

wherein Q<sub>4</sub> is



15 wherein Q<sub>5</sub> is



wherein each  $R_{17}$  is independently H; straight chained or branched  $C_1$ - $C_7$  alkyl, straight chained or branched  $C_1$ - $C_7$  monofluoroalkyl, straight chained or branched  $C_1$ - $C_7$  polyfluoroalkyl, straight chained or branched  $C_2$ - $C_7$  alkenyl, straight chained or branched  $C_2$ - $C_7$  alkynyl,  $C_5$ - $C_7$  cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_n-O-(CH_2)_m-CH_3$ ;

wherein each  $R_{20}$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl or  $C_5$ - $C_7$  cycloalkenyl; -F, -Cl, -Br, or -I;  $-NO_2$ ;  $-N_3$ ; -CN; - $OR_{21}$ ,  $-OCOR_{21}$ ,  $-COR_{21}$ ,  $-NCOR_{21}$ ,  $-N(R_{21})_2$ ,  $-CON(R_{21})_2$ , or  $-COOR_{21}$ ; aryl or heteroaryl; or two  $R_{20}$  groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each  $R_{21}$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$  cycloalkenyl or aryl;

wherein each  $R_{22}$  is independently H, F, Cl, or straight chained or branched  $C_1$ - $C_4$  alkyl;

wherein  $q$  is an integer from 2 to 4 inclusive;

wherein each  $m$  is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

wherein each p is an integer from 0 to 2 inclusive;

5 wherein U is O,  $-NR_{16}$ , S,  $C(R_{17})_2$ , or  $-NSO_2R_{16}$ ;

wherein Z is  $C_3$ - $C_{10}$  cycloalkyl,  $C_4$ - $C_7$  cyclic ether,  $C_4$ - $C_7$  cyclic thioether, aryl, or heteroaryl;

10 wherein  $R_{16}$  is straight chained or branched  $C_1$ - $C_7$  alkyl, straight chained or branched  $C_1$ - $C_7$  monofluoroalkyl, straight chained or branched  $C_1$ - $C_7$  polyfluoroalkyl, straight chained or branched  $C_2$ - $C_7$  alkenyl, straight chained or branched  $C_2$ - $C_7$  alkynyl,  
15  $C_5$ - $C_7$  cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_q-O-(CH_2)_m-CH_3$ ;

wherein B is aryl, or heteroaryl; provided however, if B is aryl or heteroaryl the carbon atom or carbon atoms ortho to the nitrogen atom of the imine bond  
20 may only be substituted with one or more of the following -F, -Cl, -Br, -I, -CN, methyl, ethyl or methoxy;

25 or a pharmaceutically acceptable salt thereof.

As used in the present invention, the term "cycloalkyl" includes  $C_3$ - $C_7$  cycloalkyl moieties which may be substituted with one or more of the  
30 following: -F,  $-NO_2$ , -CN, straight chained or branched  $C_1$ - $C_7$  alkyl, straight chained or branched  $C_1$ - $C_7$  monofluoroalkyl, straight chained or branched  $C_1$ - $C_7$  polyfluoroalkyl, straight chained or branched

5 C<sub>2</sub>-C<sub>7</sub> alkenyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkynyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>3</sub>-C<sub>7</sub> monofluorocycloalkyl, C<sub>3</sub>-C<sub>7</sub> polyfluorocycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, -N(R<sub>4</sub>)<sub>2</sub>, -OR<sub>4</sub>, -COR<sub>4</sub>, -NCOR<sub>4</sub>, -CO<sub>2</sub>R<sub>4</sub>, -CON(R<sub>4</sub>)<sub>2</sub> or (CH<sub>2</sub>)<sub>n</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-CH<sub>3</sub>.

10 As used in the present invention, the term "cycloalkenyl" includes C<sub>5</sub>-C<sub>7</sub> cycloalkenyl moieties which may be substituted with one or more of the following: -F, -Cl, -Br, -I, -NO<sub>2</sub>, -CN, straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> monofluoroalkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> polyfluoroalkyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkynyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>3</sub>-C<sub>7</sub> monofluorocycloalkyl, C<sub>3</sub>-C<sub>7</sub> polyfluorocycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, -N(R<sub>4</sub>)<sub>2</sub>, -OR<sub>4</sub>, -COR<sub>4</sub>, -NCOR<sub>4</sub>, -CO<sub>2</sub>R<sub>4</sub>, -CON(R<sub>4</sub>)<sub>2</sub> or (CH<sub>2</sub>)<sub>n</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-CH<sub>3</sub>.

20 In the present invention, the term "heteroaryl" is used to include five and six membered unsaturated rings that may contain one or more oxygen, sulfur, or nitrogen atoms. Examples of heteroaryl groups include, but are not limited to, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, and triazinyl.

30 In addition the term "heteroaryl" is used to include fused bicyclic ring systems that may contain one or more heteroatoms such as oxygen, sulfur and

nitrogen. Examples of such heteroaryl groups include, but are not limited to, indoliziny, indolyl, isoindolyl, benzo[b]furanyl, benzo[b]thiophenyl, indazolyl, benzimidazolyl, purinyl, benzoxazolyl, benzisoxazolyl, benzo[b]thiazolyl, imidazo[2,1-b]thiazolyl, cinnolinyl, quinazolinyl, quinoxalinyl, 1,8-naphthyridinyl, pteridinyl, quinolinyl, isoquinolinyl, phthalimidyl and 2,1,3-benzothiazolyl.

The term "heteroaryl" also includes those chemical moieties recited above which may be substituted with one or more of the following: -F, -Cl, -Br, -I, -NO<sub>2</sub>, -CN, straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> monofluoroalkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> polyfluoroalkyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkynyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>3</sub>-C<sub>7</sub> monofluorocycloalkyl, C<sub>3</sub>-C<sub>7</sub> polyfluorocycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, -N(R<sub>4</sub>)<sub>2</sub>, -OR<sub>4</sub>, -COR<sub>4</sub>, -NCOR<sub>4</sub>, -CO<sub>2</sub>R<sub>4</sub>, -CON(R<sub>4</sub>)<sub>2</sub> or (CH<sub>2</sub>)<sub>n</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-CH<sub>3</sub>.

The term "heteroaryl" further includes the N-oxides of those chemical moieties recited above which include at least one nitrogen atom.

In the present invention the term "aryl" is phenyl or naphthyl. The term "aryl" also includes phenyl and naphthyl which may be substituted with one or more of the following: -F, -Cl, -Br, -I, -NO<sub>2</sub>, -CN,

straight chained or branched  $C_1-C_7$  alkyl, straight  
chained or branched  $C_1-C_7$  monofluoroalkyl, straight  
chained or branched  $C_1-C_7$  polyfluoroalkyl, straight  
chained or branched  $C_2-C_7$  alkenyl, straight chained  
5 or branched  $C_2-C_7$  alkynyl,  $C_3-C_7$  cycloalkyl,  $C_3-C_7$   
monofluorocycloalkyl,  $C_3-C_7$  polyfluorocycloalkyl,  $C_5-$   
 $C_7$  cycloalkenyl,  $-N(R_4)_2$ ,  $-OR_4$ ,  $-SR_4$ ,  $-OCOR_4$ ,  $-COR_4$ ,  $-$   
 $NCOR_4$ ,  $-CO_2R_4$ ,  $-CON(R_4)_2$  or  $(CH_2)_n-O-(CH_2)_m-CH_3$ .

10

In one embodiment of any of the pharmaceutical  
compositions described herein, the compound is  
enantiomerically and diastereomerically pure. In one  
15 embodiment, the compound is enantiomerically or  
diastereomerically pure.

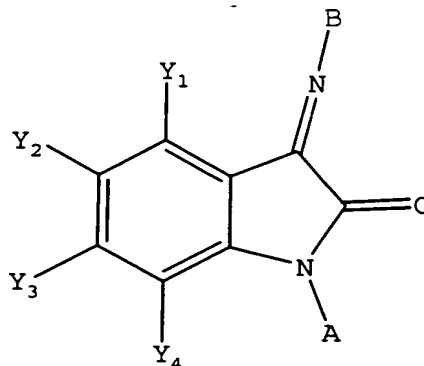
In one embodiment, the compound is a pure Z imine isomer  
or a pure Z alkene isomer.

20

In one embodiment, the compound is a pure E imine isomer  
or a pure E alkene isomer.

In one embodiment, the composition can be administered  
25 orally.

In one embodiment of the pharmaceutical composition, the  
compound has the structure:

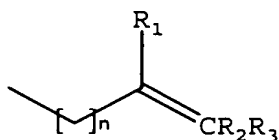


wherein each of  $Y_1$ ,  $Y_2$ ,  $Y_3$ , and  $Y_4$  is independently -  
 H; straight chained or branched  $C_1$ - $C_7$  alkyl,  $-CF_3$ , -  
 5 F,  $-Cl$ ,  $-Br$ ,  $-I$ ,  $-OR_4$ ,  $-N(R_4)_2$ , or  $-CON(R_4)_2$ ;

wherein each  $R_4$  is independently -H; straight chained  
 or branched  $C_1$ - $C_7$  alkyl,  $-CF_3$ , or phenyl;

10 wherein A is  $A'$ , straight chained or branched  $C_1$ - $C_7$   
 alkyl, aryl, heteroaryl, aryl( $C_1$ - $C_6$ )alkyl or  
 heteroaryl( $C_1$ - $C_6$ )alkyl; and

wherein  $A'$  is



15

In one embodiment, B is heteroaryl.

In one embodiment, B is aryl.

20

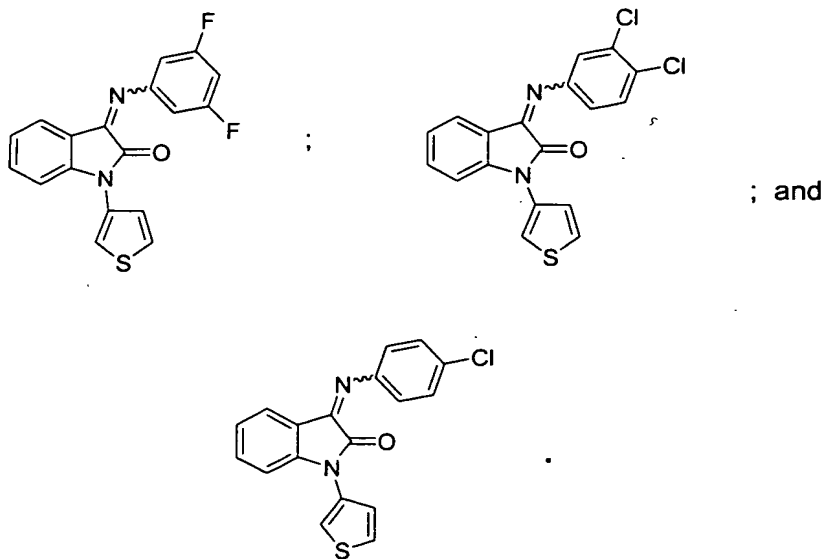
In one embodiment, B is phenyl and the phenyl is

optionally substituted with one or more of the following:  
 -F, -Cl, -Br, -CF<sub>3</sub>, straight chained or branched C<sub>1</sub>-C<sub>7</sub>  
 alkyl, -N(R<sub>4</sub>)<sub>2</sub>, -OR<sub>4</sub>, -COR<sub>4</sub>, -NCOR<sub>4</sub>, -CO<sub>2</sub>R<sub>4</sub>, or -CON(R<sub>4</sub>)<sub>2</sub>.

5 In one embodiment, A is aryl. In one embodiment, A is  
 heteroaryl.

10

In one embodiment, the compound is selected from the  
 15 group consisting of:



20



In one embodiment, B is  $Q_6$ .

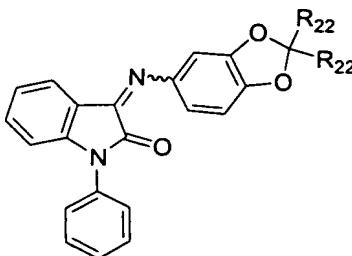
In one embodiment, A is aryl.

5

10

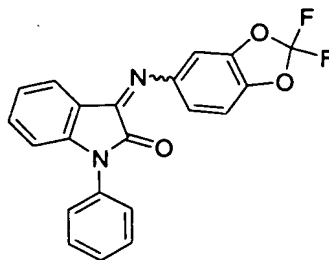
In one embodiment, the compound has the structure:

15



20

In one embodiment, the compound is:



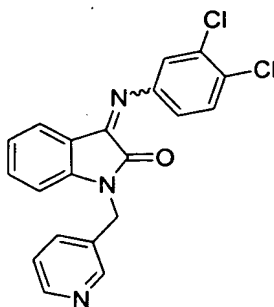
In one embodiment, B is aryl.

5

In one embodiment, A is  $(\text{CHR}_{17}) - (\text{CHR}_{17})_n - \text{Z}$ .

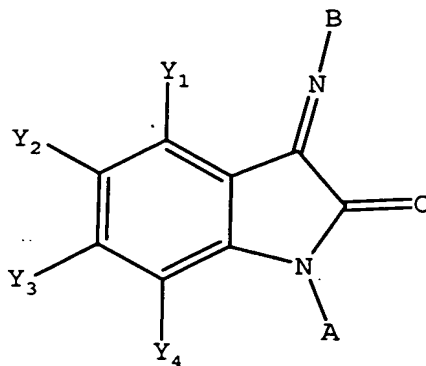
In one embodiment, the compound is:

10



The invention provides a compound having the structure:

15

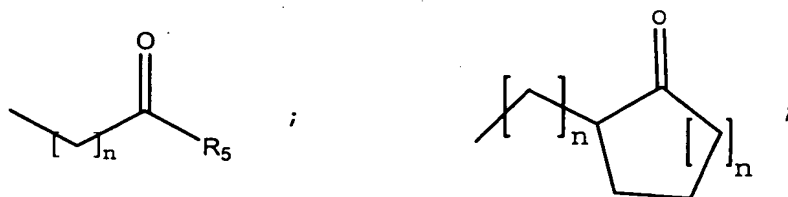


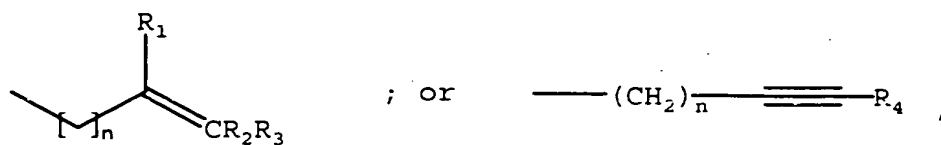
wherein each of  $Y_1$ ,  $Y_2$ ,  $Y_3$ , and  $Y_4$  is independently -  
 H; straight chained or branched  $C_1$ - $C_7$  alkyl,  
 5 monofluoroalkyl or polyfluoroalkyl; straight chained  
 or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$   
 cycloalkyl, or  $C_5$ - $C_7$  cycloalkenyl; -F, -Cl, -Br, or -  
 I; - $NO_2$ ; - $N_3$ ; -CN; - $OR_4$ , - $SR_4$ , - $OCOR_4$ , - $COR_4$ , - $NCOR_4$ , -  
 $N(R_4)_2$ , - $CON(R_4)_2$ , or - $COOR_4$ ; aryl or heteroaryl; or  
 10 any two of  $Y_1$ ,  $Y_2$ ,  $Y_3$  and  $Y_4$  present on adjacent  
 carbon atoms can constitute a methylenedioxy group;

wherein each  $R_4$  is independently -H; straight chained  
 or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or  
 15 polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$   
 alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$   
 cycloalkenyl, aryl or aryl( $C_1$ - $C_6$ )alkyl;

wherein A is A',  $Q_3$ ,  $Q_4$ ,  $Q_5$ , straight chained or  
 20 branched  $C_1$ - $C_7$  alkyl, aryl, heteroaryl, aryl( $C_1$ -  
 $C_6$ )alkyl, heteroaryl( $C_1$ - $C_6$ )alkyl, aryl substituted  
 with an aryl or heteroaryl, heteroaryl substituted  
 with an aryl or heteroaryl; or  $(CHR_{17})-(CHR_{17})_n-Z$ ;

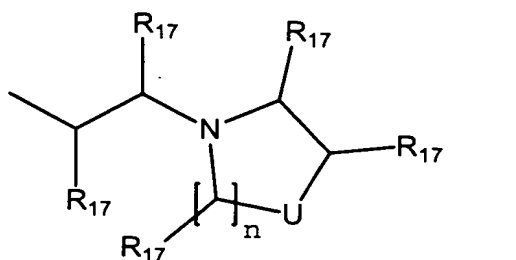
25 wherein A' is





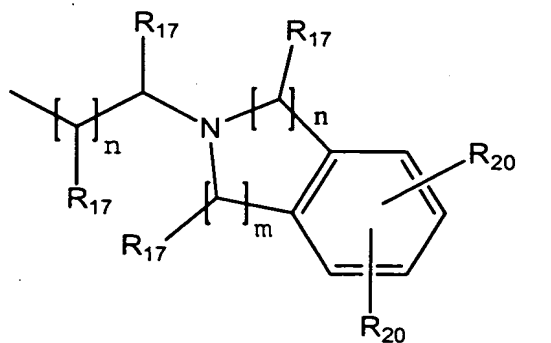
wherein  $Q_3$  is

5



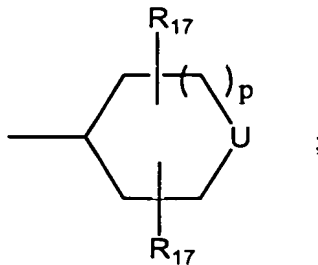
10

wherein  $Q_4$  is



15

wherein  $Q_5$  is



wherein  $R_1$  and  $R_2$  are each independently H, straight  
 5 chained or branched  $C_1$ - $C_7$  alkyl, -F, -Cl, -Br, -I, -  
 $NO_2$ , or -CN;

wherein  $R_3$  is H, straight chained or branched  $C_1$ - $C_7$   
 alkyl, -F, -Cl, -Br, -I, - $NO_2$ , -CN, - $OR_6$ , aryl or  
 10 heteroaryl;

wherein  $R_5$  is straight chained or branched  $C_1$ - $C_7$   
 alkyl, - $N(R_4)_2$ , - $OR_6$  or aryl;

15 wherein  $R_6$  is straight chained or branched  $C_1$ - $C_7$   
 alkyl or aryl;

wherein each  $R_{17}$  is independently H; straight chained  
 or branched  $C_1$ - $C_7$  alkyl, straight chained or branched  
 20  $C_1$ - $C_7$  monofluoroalkyl, straight chained or branched  
 $C_1$ - $C_7$  polyfluoroalkyl, straight chained or branched  
 $C_2$ - $C_7$  alkenyl, straight chained or branched  $C_2$ - $C_7$   
 alkynyl,  $C_5$ - $C_7$  cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_n-O-$   
 $(CH_2)_m-CH_3$ ;

25 wherein each  $R_{20}$  is independently -H; straight  
 chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or

polyfluoroalkyl; straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl or alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl or C<sub>5</sub>-C<sub>7</sub> cycloalkenyl; -F, -Cl, -Br, or -I; -NO<sub>2</sub>; -N<sub>3</sub>; -CN; -OR<sub>21</sub>, -OCOR<sub>21</sub>, -COR<sub>21</sub>, -NCOR<sub>21</sub>, -N(R<sub>21</sub>)<sub>2</sub>, -CON(R<sub>21</sub>)<sub>2</sub>, or  
 5 -COOR<sub>21</sub>; aryl or heteroaryl; or two R<sub>20</sub> groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each R<sub>21</sub> is independently -H; straight  
 10 chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl or alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, aryl or aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl;

15 wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

wherein each p is an integer from 0 to 2 inclusive;

20 wherein U is O, -NR<sub>16</sub>, S, C(R<sub>17</sub>)<sub>2</sub>, or -NSO<sub>2</sub>R<sub>16</sub>;

wherein Z is C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>4</sub>-C<sub>7</sub> cyclic ether, C<sub>4</sub>-C<sub>7</sub> cyclic thioether, aryl, or heteroaryl;

25 wherein R<sub>16</sub> is straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> monofluoroalkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> polyfluoroalkyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkynyl,  
 30 C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, -(CH<sub>2</sub>)<sub>m</sub>-Z, or (CH<sub>2</sub>)<sub>q</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-CH<sub>3</sub>;

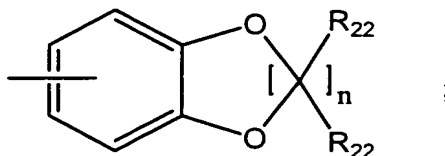
wherein q is an integer from 2 to 4 inclusive;

wherein B is aryl, heteroaryl, aryl substituted with  
 an aryl or heteroaryl, heteroaryl substituted with  
 5 an aryl or heteroaryl, tricyclic heteroaryl or Q<sub>6</sub>;  
 provided however, if B is aryl or heteroaryl the  
 carbon atom or carbon atoms ortho to the nitrogen  
 atom of the imine bond may only be substituted with  
 one or more of the following -F, -Cl, -Br, -I, -CN,  
 10 methyl, ethyl or methoxy;

wherein a tricyclic heteroaryl is a fused three  
 member aromatic system in which one or more of the  
 rings is heteroaryl; carbazole; or acridine;

15

wherein Q<sub>6</sub> is

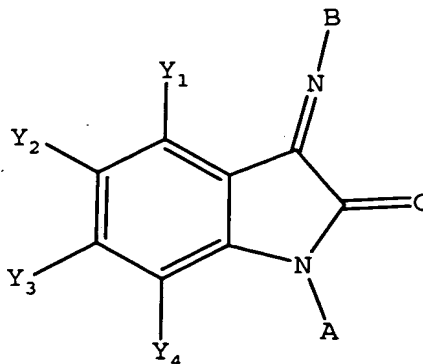


wherein each R<sub>22</sub> is independently H, F,  
 20 Cl, or straight chained or branched C<sub>1</sub>-C<sub>4</sub> alkyl;

or a pharmaceutically acceptable salt thereof.

The invention provides a compound having the structure:

25

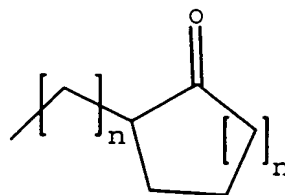
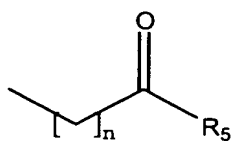


wherein each of  $Y_1$ ,  $Y_2$ ,  $Y_3$ , and  $Y_4$  is independently -  
 H; straight chained or branched  $C_1$ - $C_7$  alkyl,  
 monofluoroalkyl or polyfluoroalkyl; straight chained  
 5 or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$   
 cycloalkyl, or  $C_5$ - $C_7$  cycloalkenyl; -F, -Cl, -Br, or -  
 I; -NO<sub>2</sub>; -N<sub>3</sub>; -CN; -OR<sub>4</sub>, -SR<sub>4</sub>, -OCOR<sub>4</sub>, -COR<sub>4</sub>, -NCOR<sub>4</sub>, -  
 N(R<sub>4</sub>)<sub>2</sub>, -CON(R<sub>4</sub>)<sub>2</sub>, or -COOR<sub>4</sub>; aryl or heteroaryl; or  
 10 any two of  $Y_1$ ,  $Y_2$ ,  $Y_3$  and  $Y_4$  present on adjacent  
 carbon atoms can constitute a methylenedioxy group;

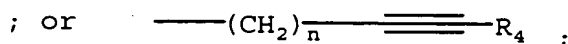
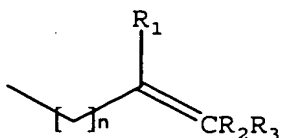
wherein each  $R_4$  is independently -H; straight chained  
 or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or  
 polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$   
 15 alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$   
 cycloalkenyl, aryl or aryl( $C_1$ - $C_6$ )alkyl;

wherein A is A', straight chained or branched  $C_1$ - $C_7$   
 alkyl, aryl, heteroaryl, aryl( $C_1$ - $C_6$ )alkyl or  
 20 heteroaryl( $C_1$ - $C_6$ )alkyl;

wherein A' is



25





5 wherein  $R_1$  and  $R_2$  are each independently H, straight  
chained or branched  $C_1$ - $C_7$  alkyl, -F, -Cl, -Br, -I, -  
 $NO_2$ , or -CN;

10 wherein  $R_3$  is H, straight chained or branched  $C_1$ - $C_7$   
alkyl, -F, -Cl, -Br, -I, - $NO_2$ , -CN, -OR<sub>6</sub> aryl or  
heteroaryl;

wherein  $R_5$  is straight chained or branched  $C_1$ - $C_7$   
alkyl, -N( $R_4$ )<sub>2</sub>, -OR<sub>6</sub> or aryl;

15 wherein  $R_6$  is straight chained or branched  $C_1$ - $C_7$   
alkyl or aryl;

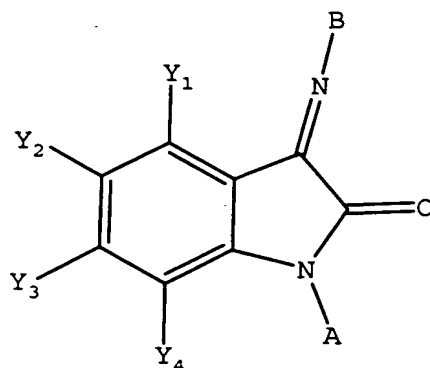
20 wherein B is aryl, or heteroaryl; provided however,  
if B is aryl or heteroaryl the carbon atom or carbon  
atoms ortho to the nitrogen atom of the imine bond  
may only be substituted with one or more of the  
following -F, -Cl, -Br, -I, -CN, methyl, ethyl or  
methoxy;

25 wherein n is an integer from 1 to 4 inclusive;

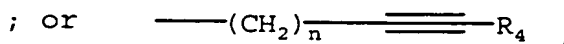
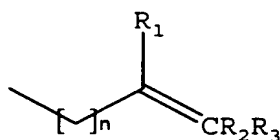
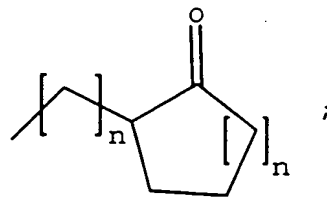
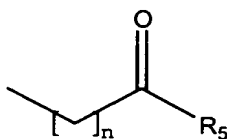
or a pharmaceutically acceptable salt thereof.

30

The invention provides a compound having the structure:



5. wherein each of Y<sub>1</sub>, Y<sub>2</sub>, Y<sub>3</sub>, and Y<sub>4</sub> is independently -  
H; straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl,  
monofluoroalkyl or polyfluoroalkyl; straight chained  
or branched C<sub>2</sub>-C<sub>7</sub> alkenyl or alkynyl; C<sub>3</sub>-C<sub>7</sub>  
cycloalkyl, or C<sub>5</sub>-C<sub>7</sub> cycloalkenyl; -F, -Cl, -Br, or -  
10 I; -NO<sub>2</sub>; -N<sub>3</sub>; -CN; -OR<sub>4</sub>, -SR<sub>4</sub>, -OCOR<sub>4</sub>, -COR<sub>4</sub>, -NCOR<sub>4</sub>, -  
N(R<sub>4</sub>)<sub>2</sub>, -CON(R<sub>4</sub>)<sub>2</sub>, or -COOR<sub>4</sub>; aryl or heteroaryl; or  
any two of Y<sub>1</sub>, Y<sub>2</sub>, Y<sub>3</sub> and Y<sub>4</sub> present on adjacent  
carbon atoms can constitute a methylenedioxy group;
- 15 wherein each R<sub>4</sub> is independently -H; straight chained  
or branched C<sub>1</sub>-C<sub>7</sub> alkyl, monofluoroalkyl or  
polyfluoroalkyl; straight chained or branched C<sub>2</sub>-C<sub>7</sub>  
alkenyl or alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>5</sub>-C<sub>7</sub>  
cycloalkenyl, aryl or aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl;
- 20 wherein A is A', straight chained or branched C<sub>1</sub>-C<sub>7</sub>  
alkyl, aryl, heteroaryl, aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl or  
heteroaryl(C<sub>1</sub>-C<sub>6</sub>)alkyl;
- 25 wherein A' is

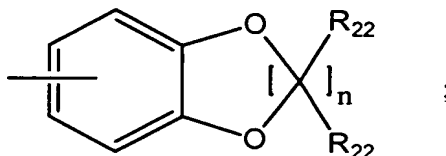


5

wherein B is aryl substituted with an aryl or  
 10 heteroaryl, heteroaryl substituted with an aryl or  
 heteroaryl, tricyclic heteroaryl or Q<sub>6</sub>;

wherein a tricyclic heteroaryl is a fused three ring  
 aromatic system in which one or more of the rings is  
 15 heteroaryl; carbazole; or acridine;

wherein Q<sub>6</sub> is



20 wherein n is an integer from 1 to 4 inclusive;

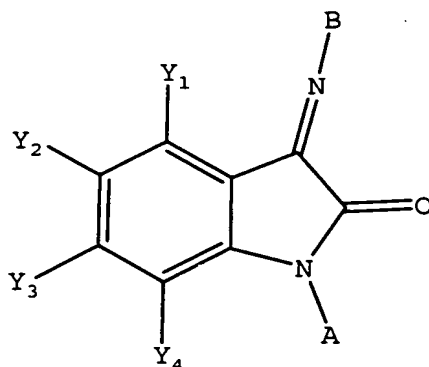
wherein each R<sub>22</sub> is independently H, F,

Cl, or straight chained or branched C<sub>1</sub>-C<sub>4</sub> alkyl;

or a pharmaceutically acceptable salt thereof.

5

The invention provides a compound having the structure:



10

wherein each of Y<sub>1</sub>, Y<sub>2</sub>, Y<sub>3</sub>, and Y<sub>4</sub> is independently -H; straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl or alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl, or C<sub>5</sub>-C<sub>7</sub> cycloalkenyl; -F, -Cl, -Br, or -I; -NO<sub>2</sub>; -N<sub>3</sub>; -CN; -OR<sub>4</sub>, -SR<sub>4</sub>, -OCOR<sub>4</sub>, -COR<sub>4</sub>, -NCOR<sub>4</sub>, -N(R<sub>4</sub>)<sub>2</sub>, -CON(R<sub>4</sub>)<sub>2</sub>, or -COOR<sub>4</sub>; aryl or heteroaryl; or any two of Y<sub>1</sub>, Y<sub>2</sub>, Y<sub>3</sub> and Y<sub>4</sub> present on adjacent carbon atoms can constitute a methylenedioxy group;

15

20

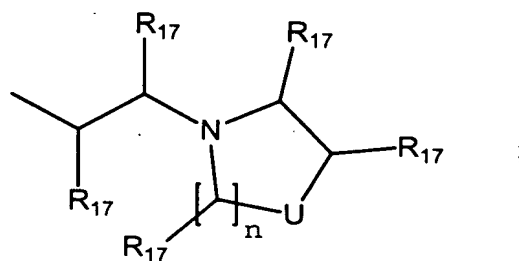
wherein each R<sub>4</sub> is independently -H; straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl or alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, aryl or aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl;

25

wherein A is Q<sub>3</sub>, Q<sub>4</sub>, Q<sub>5</sub>, aryl substituted with an

aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl, or  $(\text{CHR}_{17}) - (\text{CHR}_{17})_n - \text{Z}$ ;

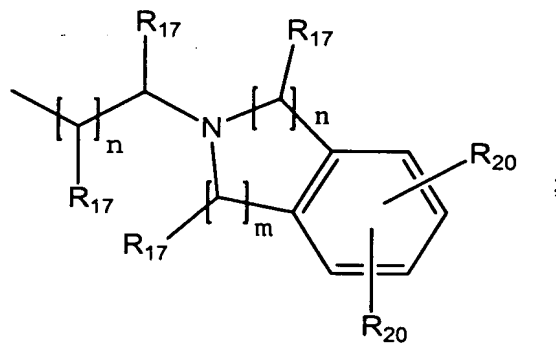
wherein  $\text{Q}_3$  is



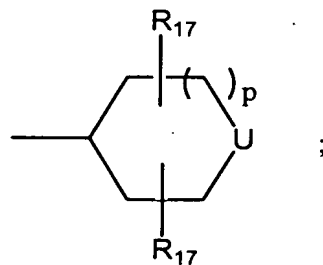
5

10

wherein  $\text{Q}_4$  is



wherein  $\text{Q}_5$  is



15

wherein each  $R_{17}$  is independently H; straight chained or branched  $C_1$ - $C_7$  alkyl, straight chained or branched  $C_1$ - $C_7$  monofluoroalkyl, straight chained or branched  $C_1$ - $C_7$  polyfluoroalkyl, straight chained or branched  $C_2$ - $C_7$  alkenyl, straight chained or branched  $C_2$ - $C_7$  alkynyl,  $C_5$ - $C_7$  cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_n-O-(CH_2)_m-CH_3$ ;

wherein each  $R_{20}$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl or  $C_5$ - $C_7$  cycloalkenyl; -F, -Cl, -Br, or -I;  $-NO_2$ ;  $-N_3$ ; -CN; - $OR_{21}$ ,  $-OCOR_{21}$ ,  $-COR_{21}$ ,  $-NCOR_{21}$ ,  $-N(R_{21})_2$ ,  $-CON(R_{21})_2$ , or  $-COOR_{21}$ ; aryl or heteroaryl; or two  $R_{20}$  groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each  $R_{21}$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$  cycloalkenyl or aryl;

wherein each  $R_{22}$  is independently H, F, Cl, or straight chained or branched  $C_1$ - $C_4$  alkyl;

wherein  $q$  is an integer from 2 to 4 inclusive;

wherein each  $m$  is an integer from 0 to 4 inclusive;

wherein each  $n$  is an integer from 1 to 4 inclusive;

wherein each p is an integer from 0 to 2 inclusive;

wherein U is O,  $-NR_{16}$ , S,  $C(R_{17})_2$ , or  $-NSO_2R_{16}$ ;

5

wherein Z is  $C_3-C_{10}$  cycloalkyl,  $C_4-C_7$  cyclic ether,  $C_4-C_7$  cyclic thioether, aryl, or heteroaryl;

10

wherein  $R_{16}$  is straight chained or branched  $C_1-C_7$  alkyl, straight chained or branched  $C_1-C_7$  monofluoroalkyl, straight chained or branched  $C_1-C_7$  polyfluoroalkyl, straight chained or branched  $C_2-C_7$  alkenyl, straight chained or branched  $C_2-C_7$  alkynyl,  $C_5-C_7$  cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_q-O-(CH_2)_m-CH_3$ ;

15

wherein B is aryl, or heteroaryl; provided however, if B is aryl or heteroaryl the carbon atom or carbon atoms ortho to the nitrogen atom of the imine bond may only be substituted with one or more of the following -F, -Cl, -Br, -I, -CN, methyl, ethyl or methoxy;

20

or a pharmaceutically acceptable salt thereof.

25

As used in the present invention, the term "cycloalkyl" includes  $C_3-C_7$  cycloalkyl moieties which may be substituted with one or more of the following: -F,  $-NO_2$ , -CN, straight chained or branched  $C_1-C_7$  alkyl, straight chained or branched  $C_1-C_7$  monofluoroalkyl, straight chained or branched  $C_1-C_7$  polyfluoroalkyl, straight chained or branched  $C_2-C_7$  alkenyl, straight chained or branched  $C_2-C_7$

30

alkynyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>3</sub>-C<sub>7</sub> monofluorocycloalkyl, C<sub>3</sub>-C<sub>7</sub> polyfluorocycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, -N(R<sub>4</sub>)<sub>2</sub>, -OR<sub>4</sub>, -COR<sub>4</sub>, -NCOR<sub>4</sub>, -CO<sub>2</sub>R<sub>4</sub>, -CON(R<sub>4</sub>)<sub>2</sub> or (CH<sub>2</sub>)<sub>n</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-CH<sub>3</sub>.

5

As used in the present invention, the term "cycloalkenyl" includes C<sub>5</sub>-C<sub>7</sub> cycloalkenyl moieties which may be substituted with one or more of the following: -F, -Cl, -Br, -I, -NO<sub>2</sub>, -CN, straight  
 10 chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> monofluoroalkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> polyfluoroalkyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkynyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>3</sub>-C<sub>7</sub>  
 15 monofluorocycloalkyl, C<sub>3</sub>-C<sub>7</sub> polyfluorocycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, -N(R<sub>4</sub>)<sub>2</sub>, -OR<sub>4</sub>, -COR<sub>4</sub>, -NCOR<sub>4</sub>, -CO<sub>2</sub>R<sub>4</sub>, -CON(R<sub>4</sub>)<sub>2</sub> or (CH<sub>2</sub>)<sub>n</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-CH<sub>3</sub>.

In the present invention, the term "heteroaryl" is  
 20 used to include five and six membered unsaturated rings that may contain one or more oxygen, sulfur, or nitrogen atoms. Examples of heteroaryl groups include, but are not limited to, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl,  
 25 triazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, and triazinyl.

In addition the term "heteroaryl" is used to include  
 30 fused bicyclic ring systems that may contain one or more heteroatoms such as oxygen, sulfur and nitrogen. Examples of such heteroaryl groups



include, but are not limited to, indoliziny, indolyl, isoindolyl, benzo[b]furanyl, benzo[b]thiophenyl, indazolyl, benzimidazolyl, purinyl, benzoxazolyl, benzisoxazolyl, benzo[b]thiazolyl, imidazo[2,1-b]thiazolyl, cinnolinyl, quinazolinyl, quinoxalinyl, 1,8-naphthyridinyl, pteridinyl, quinolinyl, isoquinolinyl, phthalimidyl and 2,1,3-benzothiazolyl.

The term "heteroaryl" also includes those chemical moieties recited above which may be substituted with one or more of the following: -F, -Cl, -Br, -I, -NO<sub>2</sub>, -CN, straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> monofluoroalkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> polyfluoroalkyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkynyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>3</sub>-C<sub>7</sub> monofluorocycloalkyl, C<sub>3</sub>-C<sub>7</sub> polyfluorocycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, -N(R<sub>4</sub>)<sub>2</sub>, -OR<sub>4</sub>, -COR<sub>4</sub>, -NCOR<sub>4</sub>, -CO<sub>2</sub>R<sub>4</sub>, -CON(R<sub>4</sub>)<sub>2</sub> or (CH<sub>2</sub>)<sub>n</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-CH<sub>3</sub>.

The term "heteroaryl" further includes the N-oxides of those chemical moieties recited above which include at least one nitrogen atom.

In the present invention the term "aryl" is phenyl or naphthyl. The term "aryl" also includes phenyl and naphthyl which may be substituted with one or more of the following: -F, -Cl, -Br, -I, -NO<sub>2</sub>, -CN, straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, straight

chained or branched C<sub>1</sub>-C<sub>7</sub> monofluoroalkyl, straight  
chained or branched C<sub>1</sub>-C<sub>7</sub> polyfluoroalkyl, straight  
chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl, straight chained  
or branched C<sub>2</sub>-C<sub>7</sub> alkynyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>3</sub>-C<sub>7</sub>  
5 monofluorocycloalkyl, C<sub>3</sub>-C<sub>7</sub> polyfluorocycloalkyl, C<sub>5</sub>-  
C<sub>7</sub> cycloalkenyl, -N(R<sub>4</sub>)<sub>2</sub>, -OR<sub>4</sub>, -SR<sub>4</sub>, -OCOR<sub>4</sub>, -COR<sub>4</sub>, -  
NCOR<sub>4</sub>, -CO<sub>2</sub>R<sub>4</sub>, -CON(R<sub>4</sub>)<sub>2</sub> or (CH<sub>2</sub>)<sub>n</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-CH<sub>3</sub>.

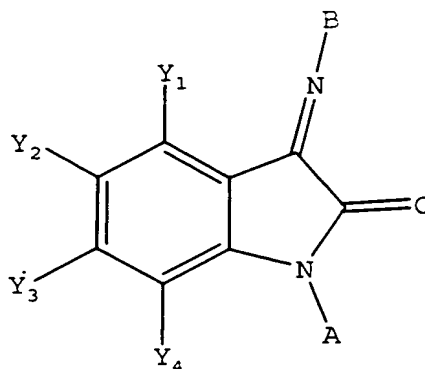
10 In one embodiment of any of the compounds described  
herein, the compound is enantiomerically and  
diastereomerically pure. In one embodiment, the compound  
is enantiomerically or diastereomerically pure.

15 In one embodiment, the compound is a pure Z imine isomer  
or a pure Z alkene isomer.

In one embodiment, the compound is a pure E imine isomer  
20 or a pure E alkene isomer.

In one embodiment, the compound can be administered  
orally.

25 In one embodiment, the compound has the structure:

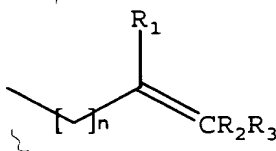


5 wherein each of  $Y_1$ ,  $Y_2$ ,  $Y_3$ , and  $Y_4$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl,  $-CF_3$ , -F, -Cl, -Br, -I,  $-OR_4$ ,  $-N(R_4)_2$ , or  $-CON(R_4)_2$ ;

wherein each  $R_4$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl,  $-CF_3$ , or phenyl;

10 wherein A is  $A'$ , straight chained or branched  $C_1$ - $C_7$  alkyl, aryl, heteroaryl, aryl( $C_1$ - $C_6$ )alkyl or heteroaryl( $C_1$ - $C_6$ )alkyl; and

wherein  $A'$  is



15

In one embodiment, B is heteroaryl.

In one embodiment, B is aryl.

20

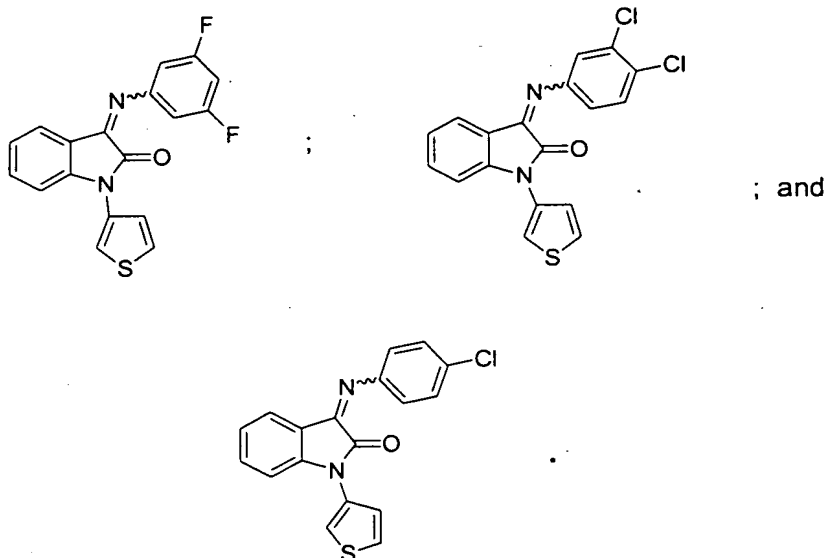
In one embodiment, B is phenyl and the phenyl is

optionally substituted with one or more of the following:  
 -F, -Cl, -Br, -CF<sub>3</sub>, straight chained or branched C<sub>1</sub>-C<sub>7</sub>  
 alkyl, -N(R<sub>4</sub>)<sub>2</sub>, -OR<sub>4</sub>, -COR<sub>4</sub>, -NCOR<sub>4</sub>, -CO<sub>2</sub>R<sub>4</sub>, or -CON(R<sub>4</sub>)<sub>2</sub>.

5 In one embodiment, A is aryl.

In one embodiment, A is heteroaryl.

10 In one embodiment, the compound is selected from the  
 group consisting of:

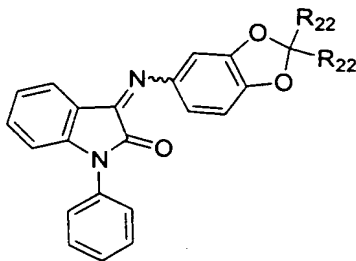


15

In one embodiment, B is Q<sub>6</sub>.

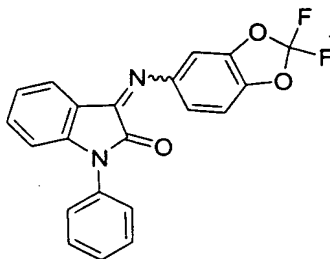
20 In one embodiment, A is aryl.

In one embodiment, the compound has the structure:



5

In one embodiment, the compound is:

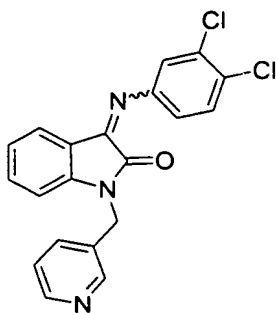


10

In one embodiment, B is aryl.

15 In one embodiment, A is  $(\text{CHR}_{17}) - (\text{CHR}_{17})_n - \text{Z}$ .

In one embodiment, the compound is:



In one embodiment, the compound is a pure Z imine isomer.

In one embodiment, the compound is a pure E imine isomer.

5.

The invention provides a pharmaceutical composition comprising a therapeutically effective amount of any of the compounds described herein and a pharmaceutically acceptable carrier.

10

The invention provides a pharmaceutical composition made by combining a therapeutically effective amount of any of the compounds described herein and a pharmaceutically acceptable carrier.

15

The invention provides a process for making a pharmaceutical composition comprising combining a therapeutically effective amount of any of the compounds described herein and a pharmaceutically acceptable carrier.

20

The invention provides a method of treating a subject suffering from depression which comprises administering to the subject an amount of any of the compounds described herein effective to treat the subject's

25

depression.

The invention provides a method of treating a subject suffering from anxiety which comprises administering to  
5 the subject an amount of any of the compounds described herein effective to treat the subject's anxiety.

The invention provides a method of treating a subject suffering from depression and anxiety which comprises  
10 administering to the subject an amount of any of the compounds described herein effective to treat the subject's depression and anxiety.

The invention provides for each pure stereoisomer of any of the compounds described herein. Such stereoisomers may include enantiomers, diastereomers, or E or Z alkene or imine isomers. The invention also provides for stereoisomeric mixtures, including racemic mixtures, diastereomeric mixtures, or E/Z isomeric mixtures. Stereoisomers can be synthesized in pure form (Nógrádi, M.; Stereoselective Synthesis, (1987) VCH Editor Ebel, H. and Asymmetric Synthesis, Volumes 3 - 5, (1983) Academic Press, Editor Morrison, J.) or they can be resolved by a variety of methods such as crystallization and chromatographic techniques (Jaques, J.; Collet, A.; Wilen, S.; Enantiomer, Racemates, and Resolutions, 1981, John Wiley and Sons and Asymmetric Synthesis, Vol. 2, 1983, Academic Press, Editor Morrison, J).

In addition the compounds of the present invention may be present as enantiomers, diastereomers, isomers or two or more of the compounds may be present to form a racemic or diastereomeric mixture.

The compounds of the present invention are preferably 80% pure, more preferably 90% pure, and most preferably 95% pure.

Included in this invention are pharmaceutically acceptable salts and complexes of all of the compounds described herein. The acids and bases from which these salts are prepared include but are not limited to the acids and bases listed herein. The acids include, but are not limited to, the following inorganic acids: hydrochloric acid, hydrobromic acid, hydroiodic acid,



sulfuric acid and boric acid. The acids include, but are not limited to, the following organic acids: acetic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, maleic acid, citric acid, methanesulfonic acid, benzoic acid, glycolic acid, lactic acid and mandelic acid. The bases include, but are not limited to ammonia, methylamine, ethylamine, propylamine, dimethylamine, diethylamine, trimethylamine, triethylamine, ethylenediamine, hydroxyethylamine, morpholine, piperazine and guanidine. This invention further provides for the hydrates and polymorphs of all of the compounds described herein.

The present invention includes within its scope prodrugs of the compounds of the invention. In general, such prodrugs will be functional derivatives of the compounds of the invention which are readily convertible in vivo into the required compound. Thus, in the present invention, the term "administering" shall encompass the treatment of the various conditions described with the compound specifically disclosed or with a compound which may not be specifically disclosed, but which converts to the specified compound in vivo after administration to the patient. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in Design of Prodrugs, ed. H. Bundgaard, Elsevier, 1985.

The present invention further includes metabolites of the compounds of the present invention. Metabolites include active species produced upon introduction of compounds of this invention into the biological milieu.

Throughout the invention, the term "binding affinity" describes the concentration of a compound required to occupy one-half of the binding sites in a receptor population, as detectable by radioligand binding. Binding affinity concentration can be represented as  $K_i$ , inhibition constant, or  $K_D$ , dissociation constant.

The term "selectivity of binding affinity" refers to the ability of a chemical compound to discriminate one receptor from another. For example, a compound showing selectivity for receptor A versus receptor B will bind receptor A at lower concentrations than those required to bind receptor B.

Therefore, the statements of the form "binds to the GAL3 receptor with a binding affinity at least ten-fold higher than" a named receptor, indicates that the binding affinity at the GAL3 receptor is at least ten-fold greater than that for a named receptor, and binding affinity measurements (i.e.  $K_i$  or  $K_D$ ) for the compound are at least ten-fold lower in numerical value.

The present invention provides a method of treating depression in a subject which comprises administering to the subject a composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a GAL3 receptor antagonist, wherein:

- (a) the GAL3 receptor antagonist binds to the human GAL3 receptor with a binding affinity at least ten-fold higher than the binding affinity with which it binds to the human GAL1 receptor;

- (b) (1) the GAL3 receptor antagonist does not inhibit the activity of central monoamine oxidase A greater than 50 percent, at a concentration of 10 $\mu$ M; and
- 5 (2) the GAL3 receptor antagonist does not inhibit the activity of central monoamine oxidase B greater than 50 percent, at a concentration of 10 $\mu$ M; and
- 10 (c) the GAL3 receptor antagonist binds to the human GAL3 receptor with a binding affinity at least ten-fold higher than the binding affinity with which it binds to each of the following transporters: serotonin transporter, norepinephrine transporter, and dopamine
- 15 transporter.

The present invention provides a method of treating anxiety in a subject which comprises administering to the subject a composition comprising a pharmaceutically

20 acceptable carrier and a therapeutically effective amount of a GAL3 receptor antagonist, wherein:

- (a) the GAL3 receptor antagonist binds to the human GAL3 receptor with a binding affinity at least ten-fold higher than the binding affinity with which it binds to
- 25 the human GAL1 receptor; and
- (b) the GAL3 receptor antagonist binds to the human GAL3 receptor with a binding affinity at least ten-fold higher than the binding affinity with which it binds to each of the following transporters: serotonin
- 30 transporter, norepinephrine transporter, and dopamine transporter.

In some embodiments of this invention, the GAL3 receptor antagonist binds to the human GAL3 receptor with a binding affinity at least 30-fold higher than the binding affinity with which it binds to the human GAL1 receptor.

5

In further embodiments of the invention, the GAL3 receptor antagonist binds to the human GAL3 receptor with a binding affinity at least 50-fold higher than the binding affinity with which it binds to the human GAL1  
10 receptor.

In other embodiments of the invention, the GAL3 receptor antagonist binds to the human GAL3 receptor with a binding affinity at least 100-fold higher than the  
15 binding affinity with which it binds to the human GAL1 receptor.

In still other embodiments of the invention, the GAL3 receptor antagonist binds to the human GAL3 receptor with  
20 a binding affinity at least 200-fold higher than the binding affinity with which it binds to the human GAL1 receptor.

For the purposes of this invention the term  
25 "pharmaceutically acceptable carrier" has been defined herein.

The term "antagonist" refers to a compound which binds to, and decreases the activity of, a receptor in the  
30 presence of an agonist. In the case of a G-protein coupled receptor, activation may be measured using an appropriate second messenger system which is coupled to

the receptor in a cell or tissue in which the receptor is expressed. Some specific but by no means limiting examples of well-known second messenger systems are adenylate cyclase, intracellular calcium mobilization, ion channel activation, guanylate cyclase, inositol phospholipid hydrolysis, and MAP kinase activation. Conversely, the term "agonist" refers to a compound which binds to, and increases the activity of, a receptor as compared with the activity of the receptor in the absence of any agonist. Methods to perform second messenger assays are described in PCT International Publication No. 97/46250 and in PCT International Publication No. 98/15570, the contents of which are hereby incorporated by reference.

In the case that a receptor has activity in the absence of an agonist (constitutive receptor activity) the antagonist may act as an inverse agonist or an allosteric modulator, as opposed to a neutral antagonist, and suppress receptor signaling independent of the agonist (Lutz and Kenakin, 1999). The categories of "antagonist compounds" are therefore seen to include 1) neutral antagonists (which block agonist actions but do not affect constitutive activity); 2) inverse agonists (which block agonist actions as well as constitutive activity by stabilizing an inactive receptor conformation); 3) and allosteric modulators (which block agonist actions to a limited extent and which may also block constitutive activity through allosteric regulation). The probability that an antagonist is neutral and therefore of "zero efficacy" is relatively low, given that this would require identical affinities for different tertiary

conformations of the receptor. Thus, Kenakin proposed in 1996 that, "with the development of sensitive test systems for the detection of inverse agonism will come a reclassification of many drugs. It might be observed that numerous previously classified neutral antagonists may be inverse agonists" (Kenakin, 1996). Indeed, there is now evidence from studies with known pharmacological agents to support the existence of inverse agonists for numerous receptors, including histamine, 5HT<sub>1A</sub>, 5HT<sub>2C</sub>, cannabinoid, dopamine, calcitonin and human formyl peptide receptors, among others (de Ligt, et al, 2000; Herrick-Davis, et al, 2000; Bakker, et al, 2000). In the case of the 5HT<sub>2C</sub> receptor, clinically effective atypical antipsychotics drugs such as sertindole, clozapine, olanzapine, ziprasidone, risperidone, zotepine, tiospirone, fluperlapine and tenilapine displayed potent inverse activity whereas typical antipsychotic drugs such as chlorpromazine, thioridazine, spiperone and thiothixene were classified as neutral antagonists (Herrick-Davis et al, 2000). In the case of the histamine H<sub>1</sub> receptor, the therapeutically used anti-allergics cetirizine, loratadine and epinastine were found to be inverse agonists. These findings further extend the idea that many compounds previously thought of as neutral antagonists will be reclassified as inverse agonists when tested in a constitutively active receptor system (de Ligt et al, 2000).

For the purpose of the claimed invention, a GAL3 antagonist useful in the treatment of depression is one which a) selectively binds to the GAL3 receptor, and b) displays antidepressant activity in the rat Forced Swim

Test. Furthermore, a GAL3 antagonist useful in the treatment of anxiety is one which a) selectively binds to the GAL3 receptor, and b) displays anxiolytic activity in the rat Social Interaction. Also for the purpose in the present invention, a GAL3 antagonist useful in the treatment of depression and anxiety, is one which a) selectively binds to the GAL3 receptor, b) displays antidepressant activity in the rat Forced Swim Test, and c) displays anxiolytic activity in the rat Social Interaction Test.

In order to test compounds for selective binding to the human GAL3 receptor the cloned cDNAs encoding both the human and rat GAL1 and GAL2 receptors have been used. The cloning and assay methods for the human and rat GAL1 receptors may be found in PCT International Publication No. WO 95/22608, the contents of which are hereby incorporated by reference. The cloning and assay methods for the human and rat GAL2 receptors may be found in PCT International Publication No. WO 97/26853, the contents of which are hereby incorporated by reference.

The present invention provides for a method of determining the binding affinity of a GAL3 antagonist, wherein the GAL3 antagonist is dissolved in a "suitable solvent". A "suitable solvent" means one which permits the measurement of binding affinity of the GAL3 antagonist to the human GAL3 receptor at concentrations less than 1  $\mu$ M, preferably less than 100 nM. Examples of solvents include, but are not limited to, DMSO, ethanol, N,N-dimethylacetamide, or water. For indolones, the

preferred solvent is 3% DMSO (final concentration in the assay). For pyrimidines, the preferred solvent is 1% ethanol/0.09% polypuronic acid F-127 (final concentration in the assay). For any other type of compounds, the preferred solvent is the solvent which permits the measurement of binding affinity of a GAL3 antagonist at the lowest concentration. Once a suitable solvent is ascertained for the binding assay of the human GAL3 receptor, the same solvent is used in assays to determine the binding affinity at the GAL1 receptor, the serotonin transporter, the norepinephrine transporter, and the dopamine transporter. A solvent of 0.4% DMSO is used in the central monoamine oxidase enzyme assay.

15 In certain embodiments, the aforementioned GAL3 receptor antagonist additionally binds to the human GAL3 receptor with a binding affinity at least ten-fold higher than the binding affinity with which it binds to the human GAL2 receptor.

20 In other embodiments, the GAL3 receptor antagonist additionally binds to the human GAL3 receptor with a binding affinity at least 30-fold higher than the binding affinity with which it binds to the human GAL2 receptor.

25 In still other embodiments, the GAL3 receptor antagonist additionally binds to the human GAL3 receptor with a binding affinity at least 50-fold higher than the binding affinity with which it binds to the human GAL2 receptor.

30 In some embodiments, the GAL3 receptor antagonist additionally binds to the human GAL3 receptor with a binding affinity at least 100-fold higher than the



binding affinity with which it binds to the human GAL2 receptor.

In further embodiments, the GAL3 receptor antagonist  
5 additionally binds to the human GAL3 receptor with a binding affinity at least 200-fold higher than the binding affinity with which it binds to the human GAL2 receptor.

10 In other embodiments, the receptor antagonist also binds to the human GAL3 receptor with a binding affinity at least ten-fold higher than the binding affinity with which it binds to each of the human 5HT<sub>1B</sub>, human 5HT<sub>1D</sub>, human 5HT<sub>1E</sub>, human 5HT<sub>1F</sub>, human 5HT<sub>2A</sub>, rat 5HT<sub>2C</sub>, human 5HT<sub>6</sub>  
15 and human 5HT<sub>7</sub> receptors.

In still another embodiment, the receptor antagonist also binds to the human GAL3 receptor with a binding affinity at least ten-fold higher than the binding affinity with  
20 which it binds to the human histamine H<sub>1</sub> receptor.

In still another embodiment, the receptor antagonist also binds to the human GAL3 receptor with a binding affinity at least ten-fold higher than the binding affinity with  
25 which it binds to the human dopamine D<sub>1</sub>, D<sub>2</sub>, D<sub>3</sub>, D<sub>4</sub> and D<sub>5</sub> receptors.

In a further embodiment, the receptor antagonist also binds to the human GAL3 receptor with a binding affinity  
30 at least ten-fold higher than the binding affinity with which it binds to the human  $\alpha_{1A}$  adrenoceptor, the human  $\alpha_{1B}$  adrenoceptor and the human  $\alpha_{1D}$  adrenoceptor.

In another embodiment, the receptor antagonist also binds to the human GAL3 receptor with a binding affinity at least ten-fold higher than the binding affinity with which it binds to the human  $\alpha_{2A}$  adrenoceptor, the human  $\alpha_{2B}$  adrenoceptor and the human  $\alpha_{2C}$  adrenoceptor.

In certain embodiments, the GAL3 receptor antagonist also binds to the human GAL3 receptor with a binding affinity less than ten-fold higher than the binding affinity with which it binds to the human 5HT<sub>4</sub> receptor.

In further embodiments, the GAL3 receptor antagonist also binds to the human GAL3 receptor with a binding affinity less than ten-fold higher than the binding affinity with which it binds to the human 5HT<sub>1A</sub> receptor.

In some embodiments the receptor antagonist does not inhibit the activity of central monoamine oxidase A greater than 30 percent. In further embodiments the receptor antagonist does not inhibit the activity of central monoamine oxidase B greater than 30 percent. In other embodiments the receptor antagonist does not inhibit the activity of central monoamine oxidase A greater than 15 percent. In still other embodiments the receptor antagonist does not inhibit the activity of central monoamine oxidase B greater than 15 percent. In still other embodiments the receptor antagonist does not inhibit the activity of central monoamine oxidase A and/or central monoamine oxidase B greater than 10 percent.

The binding properties of compounds at different receptors were determined using cultured cell lines that selectively express the receptor of interest. Cell lines were prepared by transfecting the cloned cDNA or cloned  
5 genomic DNA or constructs containing both genomic DNA and cDNA encoding the receptors as further described in the Experimental Details herein below. Furthermore, the binding interactions of compounds at different transporters and enzymes were determined using tissue  
10 preparations and specific assays as further described in the Experimental Details herein below.

In connection with this invention, a number of cloned receptors discussed herein, as stably transfected cell  
15 lines, have been made pursuant to, and in satisfaction of, the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purpose of Patent Procedure, and are made with the American Type Culture Collection, 10801 University Blvd., Manassas,  
20 Virginia 20110-2209. Specifically, these deposits have been accorded ATCC Accession Numbers as follows:

ATCC Deposits:			
Designation	Receptor	ATCC Accession No.	Date of Deposit
	human GAL1	CRL-1650	
(CHO)hGalR2-264	human GAL2	CRL 12379	07/22/1997
L-hGalR3-228	human GAL3	CRL-12373	07/01/1997
5HT <sub>1A</sub> -3	human 5-HT <sub>1A</sub>	CRL 11889	05/11/1995
Ltk-11	human 5-HT <sub>1B</sub> (formerly human 5-HT <sub>1D2</sub> )	CRL 10422	04/17/1990
Ltk-8-30-84	human 5-HT <sub>1D</sub> (formerly human 5-HT <sub>1D1</sub> )	CRL 10421	04/17/1990
5HT <sub>1E</sub> -7	human 5-HT <sub>1E</sub>	CRL 10913	11/06/1991
L-5-HT <sub>1F</sub>	human 5-HT <sub>1F</sub>	CRL 10957	12/27/1991
L-NGC-5HT <sub>2</sub>	human 5-HT <sub>2A</sub> (formerly human 5-HT <sub>2</sub> )	CRL 10287	10/31/1989
pSr-1c	rat 5-HT <sub>2C</sub> (formerly rat 5HT <sub>1C</sub> )	67636	
pBluescript-hS10	human 5-HT <sub>4</sub>	75392	12/22/1992
L-5HT-4B	human 5-HT <sub>7</sub> (formerly human 5-HT <sub>4B</sub> )	CRL 11166	10/20/1992
L- $\alpha_{1C}$	human $\alpha_{1A}$ (formerly human $\alpha_{1C}$ )	CRL11140	09/25/1992
L- $\alpha_{1B}$	human $\alpha_{1B}$	CRL11139	09/25/1992
L- $\alpha_{1A}$	human $\alpha_{1D}$ (formerly hum $\alpha_{1A}$ )	CRL11138	09/25/1992
L- $\alpha_{2A}$	human $\alpha_{2A}$	CRL11180	11/06/1992
L-NGC- $\alpha_{2B}$	human $\alpha_{2B}$	CRL10275	10/25/1989
L- $\alpha_{2C}$	human $\alpha_{2C}$	CRL11181	11/06/1992
pDopD <sub>1</sub> -GL-30	human D <sub>5</sub> (formerly hum D <sub>1<math>\beta</math></sub> )	40839	07/10/1990
pCEXV-H <sub>1</sub>	human H <sub>1</sub>	75346	11/06/1992

- 5 • The "5-HT<sub>1C</sub>", "5-HT<sub>1D1</sub>", "5-HT<sub>1D2</sub>", "5-HT<sub>4B</sub>", and "5-HT<sub>2</sub>" receptors were renamed the "5-HT<sub>2C</sub>", "5-HT<sub>1D</sub>", "5-HT<sub>1B</sub>", "5-HT<sub>7</sub>", and "5-HT<sub>2A</sub>" receptors, respectively, by the Serotonin Receptor Nomenclature Committee of the IUPHAR.
- 10 • The "human  $\alpha_{1C}$ ", "human  $\alpha_{1A}$ ", and "human D<sub>1 $\beta$</sub> " were renamed the "human  $\alpha_{1A}$ ", "human  $\alpha_{1D}$ ", and "human D<sub>5</sub>" respectively.

The following receptor sequences have been deposited with the GenBank DNA database, which is managed by the National Center for Biotechnology (Bethesda, MD).

5

GENBANK DEPOSITS		
DESIGNATION	RECEPTOR	GENBANK No.
human mRNA for D-1 receptor	human D <sub>1</sub> (formerly human D <sub>1α</sub> )	X58987
human dopamine D2 receptor (DRD2) mRNA complete cds	human D <sub>2</sub>	M29066
Rat mRNA for dopamine D3 receptor	rat D <sub>3</sub>	X53944
Homo sapiens dopamine D4 receptor (DRD4) gene (D4.4) sequence	human D <sub>4</sub>	L12397

\* The "human D<sub>1α</sub>" receptor was renamed the "human D<sub>1</sub>" receptor.

10

This invention further provides a pharmaceutical composition comprising a therapeutically effective amount of the compound of the invention and a pharmaceutically acceptable carrier. In one embodiment, the amount of the  
5 compound is an amount from about 0.01 mg to about 800 mg. In another embodiment, the amount of the compound is an amount from about 0.01 mg to about 500 mg. In another embodiment, the amount of the compound is an amount from about 0.01 mg to about 250 mg. In another embodiment,  
10 the amount of the compound is an amount from about 0.1 mg to about 60 mg. In another embodiment, the amount of the compound is an amount from about 1 mg to about 20 mg. In a further embodiment, the carrier is a liquid and the composition is a solution. In another embodiment, the  
15 carrier is a solid and the composition is a powder or tablet. In a further embodiment, the carrier is a gel and the composition is a capsule or suppository.

This invention provides a pharmaceutical composition made  
20 by combining a therapeutically effective amount of the compound of this invention and a pharmaceutically acceptable carrier.

This invention provides a process for making a  
25 pharmaceutical composition comprising combining a therapeutically effective amount of the compound of this invention and a pharmaceutically acceptable carrier.

In the subject invention a "therapeutically effective  
30 amount" is any amount of a compound which, when administered to a subject suffering from a disease against which the compounds are effective, causes

reduction, remission, or regression of the disease. In the subject application, a "subject" is a vertebrate, a mammal, or a human.

5 The present invention provides for a method of treating a subject suffering from depression which comprises administering to the subject an amount of a compound provided in the present invention effective to treat the subject's depression. The present invention also provides  
10 for a method of treating a subject suffering from anxiety which comprises administering to the subject an amount of a compound provided in the present invention effective to treat the subject's anxiety. The present invention further provides for a method of treating a subject  
15 suffering from depression and anxiety which comprises administering to the subject an amount of a compound described in the present invention effective to treat the subject's depression and anxiety.

20 The present invention provides for the use of any of the chemical compounds disclosed herein for the preparation of a pharmaceutical composition for treating an abnormality. The invention also provides for the use of a chemical compound for the preparation of a  
25 pharmaceutical composition for treating an abnormality, wherein the abnormality is alleviated by decreasing the activity of a human GAL3 receptor. In one embodiment, the abnormality is depression. In one embodiment, the abnormality is anxiety. In one embodiment, the  
30 abnormality is depression and anxiety.

In one embodiment, the chemical compound is a GAL3

receptor antagonist, wherein:

- (a) the GAL3 receptor antagonist binds to the human GAL3 receptor with a binding affinity at least ten-fold higher than the binding affinity with which it binds to the human GAL1 receptor;
- (b) (1) the GAL3 receptor antagonist does not inhibit the activity of central monoamine oxidase A greater than 50 percent, at a concentration of 10 $\mu$ M; and  
(2) the GAL3 receptor antagonist does not inhibit the activity of central monoamine oxidase B greater than 50 percent, at a concentration of 10 $\mu$ M; and
- (c) the GAL3 receptor antagonist binds to the human GAL3 receptor with a binding affinity at least ten-fold higher than the binding affinity with which it binds to each of the following transporters: serotonin transporter, norepinephrine transporter, and dopamine transporter.

In one embodiment, the chemical compound is a GAL3 receptor antagonist, wherein:

- (a) the GAL3 receptor antagonist binds to the human GAL3 receptor with a binding affinity at least ten-fold higher than the binding affinity with which it binds to the human GAL1 receptor; and
- (b) the GAL3 receptor antagonist binds to the human GAL3 receptor with a binding affinity at least ten-fold higher than the binding affinity with which it binds to each of the following transporters: serotonin transporter, norepinephrine transporter, and dopamine transporter.



transporter.

In the present invention the term "pharmaceutically acceptable carrier" is any pharmaceutical carrier known to those of ordinary skill in the art as useful in formulating pharmaceutical compositions. On December 24, 1997 the Food and Drug Administration of the United States Department of Health and Human Services published a guidance entitled "Q3C Impurities: Residual Solvent". The guidance recommends acceptable amounts of residual solvents in pharmaceuticals for the safety of the patient, and recommends the use of less toxic solvents in the manufacture of drug substances and dosage forms. Table 1 of the guidance lists "Class 1 Solvents". The guidance then states that the use of Class 1 Solvents should be avoided in the production of drug substances, excipients, or drug products unless their use can be strongly justified in a risk-benefit assessment. The guidance further states that Class 2 Solvents should be limited in order to protect patients from potentially adverse effects. The guidance characterized the following solvents as Class 1 Solvents: benzene, carbon tetrachloride, 1,2-dichloroethane, 1,1-dichloroethene, and 1,1,1-trichloroethane. The guidance characterized the following solvents as Class 2 Solvents: acetonitrile, chlorobenzene, chloroform, cyclohexane, 1,2-dichloroethene, dichloromethane, 1,2-dimethoxyethane, N,N-dimethylacetamide, N,N-dimethylformamide, 1,4-dioxane, 2-ethoxyethanol, ethyleneglycol, formamide, hexane, methanol, 2-methoxyethanol, methylbutyl ketone, methylcyclohexane, N-methylpyrrolidone, nitromethane, pyridine, sulfolane, tetralin, toluene, 1,1,2-

trichloroethene and xylene. As used in this invention the term "pharmaceutically acceptable carrier" shall not include Class 1 or Class 2 Solvents.

5 In an embodiment of the present invention, the pharmaceutical carrier may be a liquid and the pharmaceutical composition would be in the form of a solution. In another embodiment, the pharmaceutically acceptable carrier is a solid and the composition is in  
10 the form of a powder or tablet. In a further embodiment, the pharmaceutical carrier is a gel and the composition is in the form of a suppository or cream. In a further embodiment the compound may be formulated as a part of a pharmaceutically acceptable transdermal patch. In yet a  
15 further embodiment, the compound may be delivered to the subject by means of a spray or inhalant.

A solid carrier can include one or more substances which may also act as endogenous carriers (e.g. nutrient or  
20 micronutrient carriers), flavoring agents, lubricants, solubilizers, suspending agents, fillers, glidants, compression aids, binders or tablet-disintegrating agents; it can also be an encapsulating material. In powders, the carrier is a finely divided solid which is  
25 in admixture with the finely divided active ingredient. In tablets, the active ingredient is mixed with a carrier having the necessary compression properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain up to 99% of  
30 the active ingredient. Suitable solid carriers include, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose,

polyvinylpyrrolidone, low melting waxes and ion exchange resins.

Liquid carriers are used in preparing solutions, suspensions, emulsions, syrups, elixirs and pressurized compositions. The active ingredient can be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, a mixture of both or pharmaceutically acceptable oils or fats. The liquid carrier can contain other suitable pharmaceutical additives such as solubilizers, emulsifiers, buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, colors, viscosity regulators, stabilizers or osmoregulators. Suitable examples of liquid carriers for oral and parenteral administration include water (partially containing additives as above, e.g. cellulose derivatives, preferably sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols, e.g. glycols) and their derivatives, and oils (e.g. fractionated coconut oil and arachis oil). For parenteral administration, the carrier can also be an oily ester such as ethyl oleate or isopropyl myristate. Sterile liquid carriers are useful in sterile liquid form compositions for parenteral administration. The liquid carrier for pressurized compositions can be halogenated hydrocarbon or other pharmaceutically acceptable propellant.

Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilized by for example, intramuscular, intrathecal, epidural, intraperitoneal or

subcutaneous injection. Sterile solutions can also be administered intravenously. The compounds may be prepared as a sterile solid composition which may be dissolved or suspended at the time of administration using sterile water, saline, or other appropriate sterile injectable medium. Carriers are intended to include necessary and inert binders, suspending agents, lubricants, flavorants, sweeteners, preservatives, dyes, and coatings.

10

The compound can be administered orally in the form of a sterile solution or suspension containing other solutes or suspending agents (for example, enough saline or glucose to make the solution isotonic), bile salts, acacia, gelatin, sorbitan monoleate, polysorbate 80 (oleate esters of sorbitol and its anhydrides copolymerized with ethylene oxide) and the like.

The compound can also be administered orally either in liquid or solid composition form. Compositions suitable for oral administration include solid forms, such as pills, capsules, granules, tablets, and powders, and liquid forms, such as solutions, syrups, elixirs, and suspensions. Forms useful for parenteral administration include sterile solutions, emulsions, and suspensions.

Optimal dosages to be administered may be determined by those skilled in the art, and will vary with the particular compound in use, the strength of the preparation, the mode of administration, and the advancement of the disease condition. Additional factors depending on the particular subject being treated will

result in a need to adjust dosages, including subject age, weight, gender, diet, and time of administration.

This invention will be better understood from the  
5 Experimental Details which follow. However, one skilled  
in the art will readily appreciate that the specific  
methods and results discussed are merely illustrative of  
the invention as described more fully in the claims which  
follow thereafter.

## Experimental Details

### I. Synthesis of Chemical Compounds

5

The following examples are for the purpose of illustrating methods useful for making compounds of this invention.

10

15

20

25

30

**General Methods:** All reactions were performed under an Argon atmosphere and the reagents, neat or in appropriate solvents, were transferred to the reaction vessel via syringe and cannula techniques. Anhydrous solvents were purchased from the Aldrich Chemical Company and used as received. The examples described in the patent were named using the ACD/Name Program (version 4.01, Advanced Chemistry Development Inc., Toronto, Ontario, M5H2L3, Canada). The  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra were recorded at either 300 MHz (GEQE Plus) or 400 MHz (Bruker Avance) in  $\text{CDCl}_3$  as solvent and tetramethylsilane as the internal standard unless otherwise noted. Chemical shifts ( $\delta$ ) are expressed in ppm, coupling constants ( $J$ ) are expressed in Hz, and splitting patterns are described as follows: s = singlet; d = doublet; t = triplet; q = quartet; quintet; sextet; septet; br = broad; m = multiplet; dd = doublet of doublets; dt = doublet of triplets. Elemental analyses were performed by Robertson Microlit Laboratories, Inc. Unless otherwise, mass spectra were obtained using electrospray ionization (ESI, Micromass Platform II) and  $\text{MH}^+$  is reported. Thin-layer Chromatography (TLC) was carried out on glass plates pre-coated with silica gel 60 F<sub>254</sub> (0.25 mm, EM Separations Tech.). Preparative TLC was carried out on glass sheets pre-coated with silica gel GF (2 mm, Analtech). Flash column chromatography was

performed on Merck silica gel 60 (230 -400 mesh). Melting points (mp) were determined in open capillary tubes on a Mel-Temp apparatus and are uncorrected.

5 The following additional abbreviations are used: HOAc, acetic acid; DIPEA, diisopropylethylamine; DMF, *N,N*-dimethylformamide; EtOAc, ethyl acetate; MeOH, methanol; TEA, triethylamine; THF, tetrahydrofuran; All solvent ratios are volume/volume unless stated otherwise.

10

A. General Procedures for Preparing Pyrimidines

The compounds of this invention were prepared by successively displacing the three chlorine atoms of a  
15 2,4,6-trichloropyrimidine with amines. It was found that some amines (i.e. anilines) selectively displace the 2-position chlorine of 2,4,6-trichloropyrimidine, whereas other amines (e.g. piperidine) selectively displace the 4- or 6-position chlorine first (note that the 4- and 6-positions are chemically equivalent). Some amines react  
20 non-selectively at both the 2- and 4- positions of 2,4,6-trichloropyrimidine. It was also found that if the pyrimidine is substituted at the 4- or 6-position with an amine (mono- or di-substituted, or unsubstituted), then  
25 the next amine (mono- or di-substituted) undergoes substitution at the 2-position of the pyrimidine. Thus, several different Procedures were used to obtain the compounds described by this invention. The following Procedures are representative of the methods that are  
30 useful for making compounds of this invention.

## Procedure A:

4,6-DICHLORO-N-PHENYL-2-PYRIMIDINAMINE:

A solution of 2,4,6-trichloropyrimidine (5.5 g, 30 mmol) in tetrahydrofuran (15 mL) was added dropwise to a solution of aniline (2.8 mL, 1 equivalent) in tetrahydrofuran (25 mL). *N,N*-diisopropylethylamine (5.2 mL) was added and the solution was stirred at room temperature overnight. The solvent was removed and the crude material was purified by flash chromatography on silica gel. The column was eluted with 3% ethyl acetate in hexane, followed by 15% ethyl acetate in hexane. The eluent was removed, giving 4,6-dichloro-*N*-phenyl-2-pyrimidinamine (1.11 g, 4.6 mmol, 15%,  $R_f$  = 0.4 in 3% ethyl acetate in hexane).

## Procedure B:

4,6-DICHLORO-N-(3,4-DICHLOROPHENYL)-2-PYRIMIDINAMINE:

A solution of 2,4,6-trichloropyrimidine (5.00 g), 3,4-dichloroaniline (4.45 g, 1 equivalent) in 1,4-dioxane (20 mL) and *N,N*-diisopropylethylamine (10 mL) was heated at reflux with stirring for 3 hours. The solvent was removed and the crude material was purified by flash chromatography on silica gel. The column was eluted with a gradient of cyclohexane to ethyl acetate/cyclohexane (1:9). The eluent was removed, giving 4,6-dichloro-*N*-(3,4-dichlorophenyl)-2-pyrimidinamine (1.83 g, 58%,  $R_f$  = 0.39 in ethyl acetate/cyclohexane, 2:3).

## Procedure C:

6-CHLORO-N<sup>4</sup>,N<sup>4</sup>-DIMETHYL-N<sup>2</sup>-PHENYL-2,4-PYRIMIDINEDIAMINE:



Dimethylamine in tetrahydrofuran (2M, 15 mL) was added to a solution of 4,6-dichloro-*N*-phenyl-2-pyrimidinamine (0.715 g, 2.97 mmol) in tetrahydrofuran (30 mL) and *N,N*-diisopropylethylamine (0.52 mL). The resulting mixture was stirred at room temperature overnight. The solvent was removed and the crude material was purified by flash chromatography on silica gel, eluting with ethyl acetate/hexane (1:9). The eluent was removed, giving 6-chloro-*N*<sup>4</sup>,*N*<sup>4</sup>-dimethyl-*N*<sup>2</sup>-phenyl-2,4-pyrimidinediamine (0.592 g, 2.39 mmol, 80%, *R*<sub>f</sub> = 0.3).

Procedure D:

2,4-DICHLORO-6-(1-PIPERIDINYL)PYRIMIDINE: A mixture of 2,4,6-trichloropyrimidine (5.0 g, 27 mmol) and piperidine (2.3 g, 27 mmol) in tetrahydrofuran (50 mL) and *N,N*-diisopropylethylamine (3.5 g, 27 mmol) was stirred at room temperature for 24 hours. The solvent was removed and the crude material was purified by flash chromatography on silica gel. The column was eluted with a gradient of hexane to yield ethyl acetate/hexane (1:4). The eluent was removed, giving 2,4-dichloro-6-(1-piperidinyl)pyrimidine (3.67 g, 15.8 mmol, 59%, *R*<sub>f</sub> = 0.58 in ethyl acetate/hexane, 1:4).

Procedure E:

4-CHLORO-6-(1-PIPERIDINYL)-2-{4-[3-(TRIFLUOROMETHYL)-2-PYRIDINYL]-1-PIPERAZINYL}PYRIMIDINE: A mixture of 2,4-dichloro-6-(1-piperidinyl)pyrimidine (100 mg, 0.43 mmol) and 1-[3-(trifluoromethyl)pyrid-2-yl]piperazine (119 mg, 0.52 mmol) in chlorobenzene (1 mL) was heated at 140°C in a sealed tube for 24 hours. The solvent was removed and

the crude material was purified by preparative TLC, eluting with hexane/ethyl acetate (9:1). 4-chloro-6-(1-piperidinyl)-2-{4-[3-(trifluoromethyl)-2-pyridinyl]-1-piperazinyl}pyrimidine was obtained as a solid (79 mg, 0.19 mmol, 44%).

Procedure F:

N-(4-METHYLPHENYL)-6-(1-PIPERIDINYL)-2-{4-[3-(TRIFLUOROMETHYL)-2-PYRIDINYL]-1-PIPERAZINYL}-4-PYRIMIDINAMINE: A mixture of 4-chloro-6-(1-piperidinyl)-2-{4-[3-(trifluoromethyl)-2-pyridinyl]-1-piperazinyl}pyrimidine (75.0 mg, 0.176 mmol), *p*-toluidine (23.1 mg, 0.216 mmol), 1,1'-(bisdiphenylphosphino)-1,1'-binaphthol (8.4 mg), tris(dibenzylidene acetone)dipalladium(0) (8.2 mg), and sodium *tert*-butoxide (86.4 mg) in dry toluene (1 mL) was heated at 90°C in a sealed tube for 90 minutes. The solvent was removed and the crude material was purified by preparative TLC, eluting with hexane/ethyl acetate (4:1). N-(4-Methylphenyl)-6-(1-piperidinyl)-2-{4-[3-(trifluoromethyl)-2-pyridinyl]-1-piperazinyl}-4-pyrimidinamine was obtained, from the band at  $R_f = 0.4$ , as a solid (59.5 mg, 0.119 mmol, 68%).

Procedure G:

N<sup>2</sup>-ETHYL-N<sup>2</sup>-[2-(1H-3-INDOLYL)ETHYL]-N<sup>4</sup>-(4-METHYLPHENYL)-6-PIPERIDINO-2,4-PYRIMIDINEDIAMINE: A mixture of N-[4-chloro-6-(1-piperidinyl)-2-pyrimidinyl]-N-ethyl-N-[2-(1H-indol-3-yl)ethyl]amine (33.4 mg, 0.087 mmol) and *p*-toluidine (47 mg, 0.43 mmol) was heated neat under argon at 160°C in a sealed tube for 12 hours. The crude material was purified by preparative TLC, eluting with

hexane/ethyl acetate (4:1).  $N^2$ -Ethyl- $N^2$ -[2-(1H-3-indolyl)ethyl]- $N^4$ -(4-methylphenyl)-6-piperidino-2,4-pyrimidinediamine was obtained, from a band at  $R_f = 0.37$ , as a solid (15 mg, 0.033 mmol, 38%).

5

Procedure H:

2,6-DICHLORO- $N,N$ -DIMETHYL-4-PYRIMIDINAMINE: Sodium hydride (0.13 g, 0.79 mmol) was added to a solution of 2,6-dichloro-4-pyrimidinamine (0.40 g, 0.95 mmol) in dry tetrahydrofuran (5 mL) and stirred for 10 minutes, at which point gas evolution had ceased. Methyl iodide (0.06 mL, 0.95 mmol) was added and the resulting solution was stirred for 3 hours at room temperature. The solution was quenched with aqueous ammonium chloride/ammonium carbonate. The solution was extracted with ethyl acetate and the extracts were dried over sodium sulfate. The solvent was removed and the resulting crude product was purified by flash chromatography over silica gel, eluting with hexane/ethyl acetate (2:1). The desired product ( $R_f = 0.55$ ) was obtained as a white powder (70 mg, 0.36 mmol, 46%).

10  
15  
20

Procedure I:

$N$ -ETHYL-2-(1H-INDOL-3-YL)ETHANAMINE: Step 1. Acetic anhydride (1.02 g) was added dropwise to a stirring solution of tryptamine (1.60 g) in tetrahydrofuran (5 mL) at 0°C and then brought to room temperature. After 2 hours, the solvent was removed and the residue was taken up into ethyl acetate. The solution was filtered through a plug of silica gel and the solvent removed, giving  $N$ -[2-(1H-indol-3-yl)ethyl]acetyltryptamineacetamide (1.65 g, 100%).

25  
30

Step 2. Lithium aluminum hydride in tetrahydrofuran (1M, 30 mL) was added dropwise to a stirring solution of *N*-[2-(1*H*-indol-3-yl)ethylacetyltryptamineacetamide (2.02 g) in tetrahydrofuran (10 mL) at 0°C. The solution was then heated at reflux overnight. The solution was cooled to 0°C and water was very carefully added dropwise. The white solid was filtered and rinsed with ether/methanol (9:1, 2 X 25 mL). The solvent was removed from the filtrate, giving *N*-ethyl-2-(1*H*-indol-3-yl)ethanamine as a viscous pale yellow oil (1.75 g, 93%).

Procedure J:

4-CHLORO-*N*-[2-(1*H*-INDOL-3-YL)-1-METHYLETHYL]-6-(1-PIPERIDINYL)-2-PYRIMIDINAMINE: A mixture of 2,4-dichloro-6-(1-piperidinyl)pyrimidine (80 mg, 0.34 mmol),  $\alpha$ -methyltryptamine (59 mg, 0.34 mmol), and potassium carbonate (47 mg, 0.34 mmol) in chlorobenzene (1 mL) was heated at 150°C in a sealed tube for 16 hours. The solvent was removed and the crude material was purified by preparative TLC, eluting with cyclohexane/ethyl acetate (4:1). 4-Chloro-*N*-[2-(1*H*-indol-3-yl)-1-methylethyl]-6-(1-piperidinyl)-2-pyrimidinamine ( $R_f$  = 0.19) was obtained as a solid (64.5 mg, 51%).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.29 (br s, 1H), 7.68 (br d, 1H,  $J$  = 7.5), 7.32 (d, 1H,  $J$  = 7.8), 7.16 (t, 1H,  $J$  = 7.8), 7.12 (t, 1H,  $J$  = 7.8), 6.95 (d, 1H,  $J$  = 2.1), 5.87 (s, 1H), 4.89 (br d, 1H,  $J$  = 8.1), 4.36 (sextet, 1H,  $J$  = 6.6), 3.58 - 3.50 (m, 4H), 3.07 (dd, 1H,  $J$  = 14.4, 5.1), 2.83 (dd, 1H,  $J$  = 14.1, 7.2), 1.70 - 1.55 (m, 6H), 1.16 (d, 3H,  $J$  = 6.6).

## Procedure K:

N-(4-METHYLPHENYL)-2-(1-PIPERAZINYL)-6-(1-PIPERIDINYL)-4-PYRIMIDINAMINE: A solution of 2-(4-benzyl-1-piperazinyl)-N-(4-methylphenyl)-6-(1-piperidinyl)-4-pyrimidinamine (0.40 g, 0.90 mmol) and ammonium formate (0.28 g, 4.5 mmol) in methanol over 10% palladium/charcoal was stirred at 70°C for 3 hours. The solution was cooled and passed through celite. The solvent was removed, giving the desired product as a solid (0.21 g, 0.60 mmol, 66%).

## Procedure L:

N-(4-METHYLPHENYL)-2-[4-(3-METHYL-2-PYRIDINYL)-1-PIPERAZINYL]-6-(1-PIPERIDINYL)-4-PYRIMIDINAMINE: A mixture of N-(4-methylphenyl)-2-(1-piperazinyl)-6-(1-piperidinyl)-4-pyrimidinamine (100 mg, 0.284 mmol), 2-bromo-3-methylpyridine (54 mg, 0.312 mmol), 1,1'-(bis(diphenylphosphino))-1,1'-binaphthol (13 mg), tris(dibenzylidene acetone)dipalladium(0) (13 mg), and sodium *tert*-butoxide (136 mg) in dry toluene (4 mL) was heated at 90°C in a sealed tube for 2 hours. The reaction was quenched with water and the solution was extracted three times with ethyl acetate. The solvent was dried and removed. The crude material was purified by preparative TLC, eluting with hexane/ethyl acetate (2:1). N-(4-methylphenyl)-2-[4-(3-methyl-2-pyridinyl)-1-piperazinyl]-6-(1-piperidinyl)-4-pyrimidinamine was obtained, from the band at  $R_f = 0.46$ , as a solid (17.1 mg, 0.0385 mmol, 14%).

## Procedure M:

4,6-DICHLORO-2-[4-[3-(TRIFLUOROMETHYL)-2-PYRIDINYL]-1-

PIPERAZINYL}PYRIMIDINE and 2,4-DICHLORO-6-{4-[3-(TRIFLUOROMETHYL)-2-PYRIDINYL]-1-PIPERAZINYL}PYRIMIDINE:

A solution of 4-[3-(trifluoromethyl)-2-pyridinyl]-1-piperazine (127 mg, 0.66 mmol), 2,4,6-trichloropyrimidine (100 mg, 0.55 mmol) and *N,N*-diisopropylethylamine (95  $\mu$ L) in tetrahydrofuran (1 mL) was stirred at 0°C for 15 minutes. At this time, the starting material could no longer be detected by TLC. The solvent was removed and the crude material was purified by preparative TLC, eluting with ethyl acetate/hexane (1:4). Two bands were removed giving 4,6-dichloro-2-{4-[3-(trifluoromethyl)-2-pyridinyl]-1-piperazinyl}pyrimidine (41.7 mg, 0.110 mmol, 17%,  $R_f$  = 0.41), and 2,4-dichloro-6-{4-[3-(trifluoromethyl)-2-pyridinyl]-1-piperazinyl}pyrimidine (162 mg, 0.429 mmol, 65%,  $R_f$  = 0.10).

Procedure N:

4-{4-[4-CHLORO-6-(DIMETHYLAMINO)-2-PYRIMIDINYL]-1-PIPERAZINYL}PHENOL: DIPEA (4.535 g, 0.0260 mol) was added to a stirred solution of 4-*N,N*-dimethylamino-2,6-dichloropyrimidine (2.00 g, 0.0104 mol) and 4-(1-piperazinyl)phenol (2.23 g, 0.0125 mol) in THF (50 mL) at room temperature under argon. The resulting mixture was refluxed for 48 h, cooled to room temperature, quenched with water (100 mL), concentrated under reduced pressure and the crude product was redissolved in EtOAc. The organic layer was separated and washed with water (2 X 100 mL), brine (2 X 100 mL) and purified by column

chromatography on silica using EtOAc/Hexane (1:9), giving the desired product (2.77 g, 80%).

Procedure O:

5 A solution of p-toluidine (0.2 g, 1.87 mmol) in THF (2 mL) was added to a stirred suspension of NaH (0.11 g, 2.79 mmol) in anhydrous THF (2 mL) at room temperature. The resulting mixture was heated at 40 °C for 15 minutes under argon and cooled to room temperature. 6-Chloropyrimidine  
10 (0.34 g, 1.03 mmol) in THF (25 mL) was added to the above mixture and the resulting mixture was heated at reflux for 15 h. The reaction mixture was then cooled to room temperature and quenched with saturated. NH<sub>4</sub>Cl (2 drops). The crude product was concentrated under reduced pressure  
15 and redissolved in EtOAc. The organic layer was separated and washed with aqueous citric acid (2 X 100 mL), water (2 X 100 mL) and brine (2 X 100 mL). The crude product was purified by column chromatography on silica using EtOAc/hexanes (1:4), giving the desired  
20 product (0.23 g, 55%).

Procedure P:

2-(4-BENZYL-1-PIPERAZINYL)-N<sup>4</sup>-(3,4-DICHLOROPHENYL)-N<sup>6</sup>,N<sup>6</sup>-  
DIMETHYL-4,6-PYRIMIDINEDIAMINE: Potassium tert-butoxide  
25 (1.6 mmol, 1 M in 2-methyl 2-propanol) was added to a

solution of *N*-[2-(4-benzyl-1-piperazinyl)-6-chloro-4-pyrimidinyl]-*N,N*-dimethylamine (0.331 g, 0.997 mmol) and 3,4 dichloroaniline (0.178 g, 1.10 mmol) in dioxane (2 mL). Subsequently, tris(dibenzylideneacetone)dipalladium (40 mg, 0.04 mmol) and 2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl (44 mg, 0.070 mmol) were added and the mixture was stirred for 7 h at 110 °C. The resulting mixture was cooled to room temperature and concentrated under reduced pressure. The residue was treated with saturated NaHCO<sub>3</sub> (50 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 X 50 mL). The organic layer was washed with brine (2 X 100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated in vacuo, and purified by preparative TLC using hexane/EtOAc to give the desired product (300 mg, 65 %).

15

## Procedure Q:

*N*-[2-(4-BENZYL-1-PIPERAZINYL)-6-CHLORO-4-PYRIMIDINYL]-*N,N*-DIPEA (5.00 g, 40.0 mmol) was added dropwise to a solution of the *N*-(2,6-dichloro-4-pyrimidinyl)-*N,N*-dimethylamine (5.70 g, 29.6 mmol) and benzyl piperazine (6.00 g, 34.0 mmol) in *m*-xylene (15 mL). The mixture was stirred overnight at 130 °C, cooled to room temperature, treated with saturated NaHCO<sub>3</sub> (50 mL) and then extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 X 50 mL). The organic layer

20



was washed with brine (2 X 100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated in vacuo. The crude product was purified by chromatography on silica using EtOAc/hexane (1:3), giving the desired product (6.8 g, 20 mmol, 67%).

5

Procedure R:

N<sup>4</sup>, N<sup>4</sup>-DIMETHYL-N<sup>6</sup>-(4-METHYLPHENYL)-N<sup>2</sup>-(2-PHENYLETHYL)-

2,4,6-PYRIMIDINETRIAMINE: A mixture of N-[4-(dimethylamino)-6-(4-toluidino)-2-pyrimidinyl]-2-

10 phenylacetamide (60 mg, 0.166 mmol), and LAH (1mL, 1M in THF) in THF (10 mL) was refluxed for 3h.

The crude product was concentrated in vacuo and treated with saturated NaHCO<sub>3</sub> (50 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 X 50 mL). The organic layer was washed with brine (2 X 15 100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated in vacuo. The crude product was purified by preparative TLC using hexane/EtOAc (1:3), giving the desired product (30 mg, 52 %).

20 Procedure S:

N-[4-(DIMETHYLAMINO)-6-(4-TOLUIDINO)-2-PYRIMIDINYL]-2-

PHENYLACETAMIDE: A mixture of N<sup>4</sup>, N<sup>4</sup>-dimethyl-N<sup>6</sup>-(4-methylphenyl)-2,4,6-pyrimidinetriamine (122 mg, 0.50 mmol), phenylacetyl chloride (84 mg, 0.55 mmol), and

triethylamine (100 mg, 1.00 mmol) in  $\text{CH}_2\text{Cl}_2$  was stirred at room temperature for 16h. The crude product was concentrated *in vacuo* and treated with saturated  $\text{NaHCO}_3$  (50 mL) and extracted with  $\text{CH}_2\text{Cl}_2$  (3 X 50 mL). The organic layer was washed with brine (2 X 100 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated *in vacuo*. The crude product was purified by preparative TLC using hexane/EtOAc (1:3), giving the desired product (60 mg, 33 %).

Procedure T:

A mixture of  $N^4$ -(3-methoxyphenyl)- $N^6,N^6$ -dimethyl-2-[4-(2-thienylcarbonyl)-1-piperazinyl]-4,6-pyrimidinediamine (28 mg, 0.06 mmol) and LAH (300  $\mu\text{L}$  1M, 0.3 mmol) in THF (10 mL) was refluxed for 16 h. The crude product was concentrated *in vacuo* and treated with saturated  $\text{NaHCO}_3$  (50 mL) and extracted with EtOAc (3 X 50 mL). The organic layer was washed with brine (2 X 100 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated *in vacuo*. The crude product was purified by preparative TLC using hexane/EtOAc (1:3), giving the desired product (20 mg, 39 %).

Procedure U:

2-[4-(3-METHOXYBENZYL)-1-PIPERAZINYL]-N<sup>4</sup>-(3-

METHOXYPHENYL)-N<sup>6</sup>,N<sup>6</sup>-DIMETHYL-4,6-PYRIMIDINEDIAMINE: A

5 solution of N<sup>4</sup>-(3-methoxyphenyl)-N<sup>6</sup>,N<sup>6</sup>-dimethyl-2-(1-piperaziny)-4,6-pyrimidinediamine (36 mg, 0.1 mmol),  
 DIPEA (52 mg, 0.4 mmol), and 1-(chloromethyl)-3-methoxybenzene (20 mg, 0.13 mmol) in 5 mL of dioxane was  
 stirred at 100 °C for 16 h. The crude product was  
 concentrated *in vacuo* and treated with saturated NaHCO<sub>3</sub>  
 (50 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 X 50 mL). The  
 10 organic layer was washed with brine (2 X 100 mL), dried  
 over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo*. The crude product  
 was purified by chromatography on silica using  
 hexane/EtOAc (1:3), giving the desired product (32 mg, 70  
 %).

15

Procedure V:

6-CHLORO-N<sup>4</sup>-(4-METHYLPHENYL)-2,4-PYRIMIDINEDIAMINE: A

mixture of 4,6-dichloro-2-pyrimidinamine (1.64 g, 0.01  
 mol), *p*-toluidine (1.07 g, 0.01 mol) in dioxane (2 mL)  
 20 was heated in a sealed tube for 30 minutes at 140 °C. The  
 crude product was treated with NaOH (50 mL, 2M) and  
 extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 X 50 mL). The organic layer was  
 washed with brine (2 X 100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>,  
 filtered, and concentrated *in vacuo*. The crude product

was purified by chromatography on silica using hexane/EtOAc (1:3), giving the desired product (2 g, 78 %).

5 Procedure W:

$N^4$ -(3-METHOXYPHENYL)- $N^6,N^6$ -DIMETHYL-2-[4-(2-THIENYLCARBONYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE: A mixture of 2-thiophenecarboxylic acid (15 mg, 0.12 mmol), DIPEA (129 mg, 1.00 mmol) and O-(7-  
10 azabenzotriazol-1-yl)N,N,N',N'-tetramethyluronium hexafluorophosphate (44 mg, 0.12 mmol) in DMF (5 mL) was stirred at room temperature for 30 minutes.  $N^4$ -(3-methoxyphenyl)- $N^6,N^6$ -dimethyl-2-(1-piperazinyl)-4,6-pyrimidinediamine (36 mg, 0.10 mmol) was added to the  
15 above mixture and stirred at room temperature for 16 h. The crude product was treated with saturated  $\text{NaHCO}_3$  (50 mL) and extracted with EtOAc (3 X 50 mL). The organic layer was washed with brine (2 X 100 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated *in vacuo*. The crude  
20 product was purified by chromatography on silica using hexane/EtOAc (1:3), giving the desired product (25 mg, 57 %).

Procedure X:

2-(4-BENZYL-1-PIPERAZINYL)-N<sup>4</sup>-(3-METHOXYPHENYL)-N<sup>6</sup>,N<sup>6</sup>-

DIMETHYL-4,6-PYRIMIDINEDIAMINE: A mixture of N<sup>4</sup>-(3-methoxyphenyl)-N<sup>6</sup>,N<sup>6</sup>-dimethyl-2-(1-piperazinyl)-4,6-pyrimidinediamine (36 mg, 0.10 mmol) and benzaldehyde (11 mg, 0.1 mmol) in a solution of methanol (5 mL) and acetic acid (0.5 mL) was stirred at room temperature for 1 h. Sodium cyanoborohydride (7 mg, 0.1 mmol) was added to the above solution and stirred at room temperature for 16 h. The crude product was treated with saturated NaHCO<sub>3</sub> (50 mL) and extracted with EtOAc (3 X 50 mL). The organic layer was washed with brine (2 X 50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. The crude product was purified by chromatography on silica using hexane/EtOAc (1:3), giving the desired product (8 mg, 40 %).

Procedure Y:

2-[4-(4-BROMOPHENYL)-1-PIPERAZINYL]-N<sup>4</sup>-(3-METHOXYPHENYL)-

N<sup>6</sup>,N<sup>6</sup>-DIMETHYL-4,6-PYRIMIDINEDIAMINE: A mixture of N<sup>4</sup>-(3-methoxyphenyl)-N<sup>6</sup>,N<sup>6</sup>-dimethyl-2-(1-piperazinyl)-4,6-pyrimidinediamine (36 mg, 0.1 mmol), 1-bromo-4-fluorobenzene (20 mg, 0.13 mmol) was heated at 100 °C for 1 h. The crude product was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (0.5 mL)

and purified by preparative TLC using 5 % methanol in EtOAc, giving the desired product (20 mg, 40 %).

Procedure Z:

5     2-[4-(2-METHOXYBENZYL)-1-PIPERAZINYL]-N<sup>4</sup>,N<sup>4</sup>-DIMETHYL-N<sup>6</sup>-(4-METHYLPHENYL)-4,6-PYRIMIDINEDIAMINE: A mixture of N<sup>4</sup>,N<sup>4</sup>-dimethyl-N<sup>6</sup>-(4-methylphenyl)-2-(1-piperaziny)-4,6-pyrimidinediamine (30 mg, 0.086 mmol), 1-(chloromethyl)-2-methoxybenzene (17 mg, 0.1 mmol) and triethylamine  
10     (200 mg, 2 mmol) in 1 DMF (1 mL) heated by microwave at 200 °C for 12 minutes. The crude product was treated with saturated NaHCO<sub>3</sub> (50 mL) and extracted with EtOAc (3 X 50 mL). The organic layer was washed with brine (2 X 100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated in  
15     *vacuo*. The crude product was purified by chromatography on silica using hexane/EtOAc (1:3), giving the desired product (10 mg, 27 %).

Procedure AA:

20     N<sup>4</sup>-(3-METHOXYPHENYL)-N<sup>6</sup>,N<sup>6</sup>-DIMETHYL-2-[4-(2-THIENYLCARBONYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE:  
A solution of N<sup>4</sup>-(3-methoxyphenyl)-N<sup>6</sup>,N<sup>6</sup>-dimethyl-2-(1-piperaziny)-4,6-pyrimidinediamine (33 mg, 0.1 mmol), 2-thiophenecarbonyl chloride (20 mg, 0.14 mmol), and

triethylamine (40 mg, 0.4 mmol) in  $\text{CH}_2\text{Cl}_2$  (5 mL) was stirred at room temperature for 16 h. The crude product was concentrated *in vacuo* and treated with saturated  $\text{NaHCO}_3$  (50 mL) and extracted with  $\text{CH}_2\text{Cl}_2$  (3 X 50 mL). The organic layer was washed with brine (2 X 100 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated *in vacuo*. The crude product was purified by chromatography on silica using hexane/EtOAc (1:3), giving the desired product as a pale red oil (35 mg, 80 %).

Procedure BB:

$N^4, N^4$ -DIMETHYL- $N^6$ -(4-METHYLPHENYL)-2,4,6-

PYRIMIDINETRIAMINE: A mixture of 6-chloro- $N^4$ -(4-methylphenyl)-2,4-pyrimidinediamine (1.5 g, 6.4 mmol), and  $N,N$ -dimethylamine hydrochloride (0.56 g, 7 mmol) and triethylamine (1.4 g, 14 mmol) in DMF (2 mL), was heated at 170 °C for 16 h. The product was filtered out and the organic layer was treated with saturated  $\text{NaHCO}_3$  (50 mL) and extracted with EtOAc (3 X 50 mL). The organic layer was washed with brine (2 X 100 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated *in vacuo*. The crude product was purified by chromatography on silica using hexane/EtOAc (1:3), giving the desired product (0.6 g, 40 %).

Procedure CC:

N-(4-METHYLPHENYL)-2-[4-(1-OXIDO-2-PYRIDINYL)-1-

PIPERAZINYL]-6-(1-PIPERIDINYL)-4-PYRIMIDINAMINE:

A

5 solution of 3-chloroperbenzoic acid (450 mg, 2.6 mmol),  
and 30 % H<sub>2</sub>O<sub>2</sub> (0.1 mL) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) was added to a  
solution of N-(4-methylphenyl)-6-(1-piperidinyl)-2-[4-(2-  
pyridinyl)-1-piperazinyl]-4-pyrimidinamine (150 mg, 0.300  
mmol) in CH<sub>2</sub>Cl<sub>2</sub> at 0 °C. The resulting mixture was  
10 gradually warmed to room temperature and stirred for 24  
h, crude product was treated with saturated NaHCO<sub>3</sub> (50 mL)  
and extracted with EtOAc (3 X 50 mL). Combined organic  
layers were washed with brine (2 X 50 mL), dried over  
Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated in vacuo, and purified by  
15 chromatography on silica using hexane/EtOAc (1:3) to give  
the desired product.

Piperazines that were not commercially available were  
synthesized according to the method previously described  
20 (Ennis and Ghazal, 1992).

The following are examples to illustrate the compounds of  
this invention. Procedures A - BB as described above,  
were used and any modifications are noted in parentheses.

25

Example 1: N<sup>2</sup>-CYCLOHEXYL-N<sup>2</sup>-METHYL-N<sup>4</sup>-(4-METHYLPHENYL)-6-



(1-PIPERIDINYL)-2,4-PYRIMIDINEDIAMINE: Prepared by Procedures D, G (for substitution with cyclohexylamine), and G.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.22 (d, 2H,  $J = 7.8$ ), 7.12 (d, 2H,  $J = 7.8$ ), 5.29 (s, 1H), 4.43 (br s, 1H), 3.55 - 3.44 (m, 5H), 3.01 (s, 3H), 2.33 (s, 3H), 2.00 - 1.05 (m, 16H).

Example 2:  $N^2$ -CYCLOHEXYL- $N^2$ -(2-METHOXYETHYL)- $N^4$ -(4-METHYLPHENYL)-6-(1-PIPERIDINYL)-2,4-PYRIMIDINEDIAMINE:

Prepared by Procedures D, J (130°C), and F (2 hours).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.25 (d, 2H,  $J = 8.1$ ), 7.10 (d, 2H,  $J = 8.1$ ), 6.17 (br s, 1H), 5.31 (s, 1H), 4.58 - 4.43 (m, 1H), 3.61 - 3.57 (m, 4H), 3.52 - 3.48 (m, 4H), 3.39 (s, 3H), 2.31 (s, 3H), 1.83 - 1.75 (m, 4H), 1.70 - 1.50 (m, 7H), 1.43 - 1.37 (m, 4H), 1.19 - 1.05 (m, 1H); ESI-MS  $m/z$  424 ( $\text{MH}^+$ ).

Example 3:  $N^4$ -(4-METHYLPHENYL)- $N^2$ -PHENYL-6-(1-PIPERIDINYL)-2,4-PYRIMIDINEDIAMINE: Prepared by

Procedures A, B (for substitution with aniline), and E (100°C, for substitution with piperidine).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.58 (d, 2H,  $J = 8.7$ ), 7.26 (t, 2H,  $J = 7.8$ ), 7.19 (d, 2H,  $J = 8.7$ ), 7.15 (d, 2H,  $J = 7.8$ ), 6.95 (t, 1H,  $J = 7.8$ ), 6.82 (br s, 1H), 6.48 (br s, 1H), 5.49 (s, 1H), 3.56 - 3.46 (m, 4H), 2.34 (s, 3H), 1.67 - 1.52 (m, 6H); ESI-MS  $m/z$  360 ( $\text{MH}^+$ ).

Example 4:  $N^2, N^4$ -DI(4-METHYLPHENYL)-6-PIPERIDINO-2,4-PYRIMIDINEDIAMINE: Prepared by Procedures D and G (100°C,

12 hours, for substitution of *p*-toluidine at C2 and C4 of the pyrimidine).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.47 (d, 2H,  $J = 8.3$ ), 7.20 (d, 2H,  $J = 7.8$ ), 7.15 (d, 2H,  $J = 8.3$ ),

7.10 (d, 2H,  $J = 8.3$ ), 6.79 (br s, 1H), 6.46 (br s, 1H), 5.52 (s, 1H), 3.51 (t, 4H,  $J = 4.6$ ), 2.36 (s, 3H), 2.31 (s, 3H), 1.69 - 1.53 (m, 6H); ESI-MS  $m/z$  374 ( $MH^+$ ).

5 Example 5:  $N^2$ -(4-CHLOROPHENYL)- $N^4$ -(4-METHYLPHENYL)-6-(1-PIPERIDINYL)-2,4-PYRIMIDINEDIAMINE: Prepared by Procedures D, G (for substitution with 4-chloroaniline), and G (3.5 hours).  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  8.79 (br s, 1H), 7.72 (br s, 1H), 7.54 (d, 2H,  $J = 8.3$ ), 7.28 - 7.17  
10 (m, 6H), 5.36 (s, 1H), 3.61 - 3.46 (m, 4H), 2.36 (s, 3H), 1.76 - 1.53 (m, 6H); ESI-MS  $m/z$  393 ( $MH^+$  with  $^{35}Cl$ ), 395 ( $MH^+$  with  $^{37}Cl$ ).

15 Example 6:  $N^2$ -METHYL- $N^4$ -(4-METHYLPHENYL)- $N^2$ -PHENYL-6-(1-PIPERIDINYL)-2,4-PYRIMIDINEDIAMINE: Prepared by Procedures D, G (140°C, 90 minutes, for substitution with aniline), and G (3.5 hours).  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  7.42 - 7.33 (m, 4H), 7.18 - 7.14 (overlapping t at 7.16 & d at 7.15, 3H), 7.07 (d, 2H,  $J = 7.8$ ), 6.25 (br s, 1H),  
20 5.41 (s, 1H), 3.54 (s, 3H), 3.50 - 3.42 (m, 4H), 2.33 (s, 3H), 1.68 - 1.50 (m, 6H); ESI-MS  $m/z$  374 ( $MH^+$ ).

25 Example 7:  $N^2$ -METHYL- $N^2,N^4$ -DI(4-METHYLPHENYL)-6-(1-PIPERIDINYL)-2,4-PYRIMIDINEDIAMINE: Prepared by Procedures D, G (180°C, 10 hours, for substitution with *N*-methyl-*p*-toluidine), and G (140°C).  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  7.27 - 7.04 (m, 8H), 6.19 (br s, 1H), 5.38 (s, 1H), 3.52 (s, 3H), 3.48 - 3.41 (m, 4H), 2.38 (s, 3H),  
30 2.31 (s, 3H), 1.67 - 1.49 (m, 6H); ESI-MS  $m/z$  388 ( $MH^+$ ).

Example 8:  $N^2$ -[2-(5-METHYL-1*H*-3-INDOLYL)ETHYL]- $N^4$ -(4-

METHYLPHENYL)-6-(1-PIPERIDINYL)-2,4-PYRIMIDINEDIAMINE:

Prepared by Procedures D, J, and G (160°C, 12 hours). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.05 (br s, 1H), 7.43 (s, 1H), 7.23 (d, 1H, *J* = 8.4), 7.15 (d, 2H, *J* = 8.4), 7.10 (d, 2H, *J* = 8.4), 7.00 (d, 1H, *J* = 8.4), 6.98 (s, 1H), 6.43 (br s, 1H), 5.37 (s, 1H), 4.86 (br t, 1H, *J* = 7.1), 3.70 (q, 2H, *J* = 7.1), 3.52 - 3.43 (m, 4H), 3.02 (t, 2H, *J* = 7.1), 2.46 (s, 3H), 2.32 (s, 3H), 1.67 - 1.49 (m, 6H); ESI-MS *m/z* 441 (MH<sup>+</sup>).

Example 9: N<sup>2</sup>-[2-(5-METHOXY-1H-3-INDOLYL)ETHYL]-N<sup>4</sup>-(4-METHYLPHENYL)-6-(1-PIPERIDINYL)-2,4-PYRIMIDINEDIAMINE:

Prepared by Procedures D, E (160°C, 36 hours), and G. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.00 (br s, 1H), 7.15 (d, 2H, *J* = 8.4), 7.12 (d, 2H, *J* = 8.4), 7.08 - 7.04 (m, 3H), 6.85 (dd, 1H, *J* = 8.8, 2.6), 6.48 (br s, 1H), 5.36 (s, 1H), 4.96 (br s, 1H), 3.85 (s, 3), 3.72 - 3.67 (m, 2H), 3.55 - 3.45 (m, 4H), 3.02 (t, 2H, *J* = 6.9), 2.32 (s, 3H), 1.68 - 1.49 (m, 6H); ESI-MS *m/z* 457 (MH<sup>+</sup>).

Example 10: N<sup>2</sup>-[2-(1H-3-INDOLYL)ETHYL]-N<sup>4</sup>-(4-METHYLPHENYL)-6-(1-PIPERIDINYL)-2,4-PYRIMIDINEDIAMINE:

Prepared by Procedures D, E (100°C), and G (150°C). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.34 (br s, 1H), 7.63 (d, 1H, *J* = 7.8), 7.31 (d, 1H, *J* = 7.8), 7.23 - 7.09 (m, 6H), 6.94 (s, 1H), 6.60 (br s, 1H), 5.36 (s, 1H), 4.95 (t, 1H, *J* = 6.3), 3.68 (dt, 2H, *J* = 6.3, 6.9), 3.48 - 3.44 (m, 4H), 3.01 (t, 2H, *J* = 6.9), 2.31 (s, 3H), 1.65 - 1.48 (m, 6H); ESI-MS *m/z* 427 (MH<sup>+</sup>).

Example 11: N<sup>2</sup>-[2-(1H-3-INDOLYL)ETHYL]-N<sup>2</sup>-METHYL-N<sup>4</sup>-(4-METHYLPHENYL)-6-(1-PIPERIDINYL)-2,4-PYRIMIDINEDIAMINE:

Prepared by Procedures D, E (160°C, 4 hours), and F (12 hours). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.02 (br s, 1H), 7.71 (d, 1H, *J* = 7.8), 7.36 (d, 1H, *J* = 7.8), 7.22 (d, 2H, *J* = 7.8), 7.20 (t, 1H, *J* = 7.8), 7.17 - 7.09 (m, 3H), 7.03 (s, 1H), 6.40 (br s, 1H), 5.35 (s, 1H), 3.91 (t, 2H, *J* = 7.8), 3.56 - 3.46 (m, 4H), 3.16 (s, 3H), 3.09 (t, 2H, *J* = 7.8), 2.33 (s, 3H), 1.70 - 1.52 (m, 6H); ESI-MS *m/z* 441 (MH<sup>+</sup>).

10 Example 12: N<sup>2</sup>-[2-(1H-INDOL-3-YL)ETHYL]-N<sup>2</sup>-METHYL-N<sup>4</sup>-PHENETHYL-6-(1-PIPERIDINYL)-2,4-PYRIMIDINEDIAMINE:

Prepared by Procedures D, E (160°C, 12 hours), and G. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.00 (br s, 1H), 7.71 (d, 1H, *J* = 7.8), 7.34 (t, 2H, *J* = 7.8), 7.24 - 7.15 (m, 5H), 7.08 (t, 1H, *J* = 7.8), 6.98 (s, 1H), 4.95 (s, 1H), 4.39 (br s, 1H), 3.88 (t, 2H, *J* = 7.8), 3.57 - 3.48 (m, 6H), 3.12 (s, 3H), 3.05 (t, 2H, *J* = 7.8), 2.89 (t, 2H, *J* = 7.8), 1.68 - 1.53 (m, 6H); ESI-MS *m/z* 455 (MH<sup>+</sup>).

20 Example 13: N<sup>2</sup>-[2-(1H-INDOL-3-YL)ETHYL]-N<sup>2</sup>-METHYL-N<sup>4</sup>-(2-NAPHTHYL)-6-(1-PIPERIDINYL)-2,4-PYRIMIDINEDIAMINE:

Prepared by Procedures D, E (160°C, 12 hours, for substitution with *N*-methyltryptamine), and E (160°C, 12 hours). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.95 (br s, 1H), 7.92 (s, 1H), 7.78 - 7.75 (m, 3H), 7.72 (d, 1H, *J* = 8.1), 7.46 - 7.41 (m, 2H), 7.37 (d, 2H, *J* = 8.4), 7.20 (t, 1H, *J* = 7.8), 7.11 (t, 1H, *J* = 7.8), 7.01 (s, 1H), 6.42 (br s, 1H), 5.45 (s, 1H), 3.95 (t, 2H, *J* = 7.8), 3.56 - 3.49 (m, 4H), 3.19 (s, 3H), 3.11 (t, 2H, *J* = 7.8), 1.62 - 1.59 (m, 6H); ESI-MS *m/z* 477 (MH<sup>+</sup>).

30 Example 14: N<sup>4</sup>-(3-FLUOROPHENYL)-N<sup>2</sup>-[2-(1H-INDOL-3-

YL)ETHYL]-N<sup>2</sup>-METHYL-6-(1-PIPERIDINYL)-2,4-

PYRIMIDINEDIAMINE: Prepared by Procedures D, E (160°C, 12 hours, for substitution with *N*-methyltryptamine), and G. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.97 (br s, 1H), 7.71 (d, 1H, *J* = 7.8), 7.41 (dt, 1H, *J* = 9.5, 1.0), 7.34 (d, 1H, *J* = 7.8), 7.22 - 7.06 (m, 4H), 7.02 - 7.00 (s at 7.02 & d at 7.01 overlapping, 2H), 7.01 (s, 1H), 6.33 (br s, 1H), 5.34 (s, 1H), 3.90 (t, 2H, *J* = 7.8), 3.58 - 3.50 (m, 4H), 3.16 (s, 3H), 3.08 (t, 2H, *J* = 7.8), 1.70 - 1.54 (m, 6H); ESI-MS *m/z* 445 (MH<sup>+</sup>).

Example 15: N<sup>4</sup>-(3,4-DIFLUOROPHENYL)-N<sup>2</sup>-[2-(1H-INDOL-3-YL)ETHYL]-N<sup>2</sup>-METHYL-6-(1-PIPERIDINYL)-2,4-

PYRIMIDINEDIAMINE: Prepared by Procedures D, E (160°C, 12 hours, for substitution with *N*-methyltryptamine), and G. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.99 (br s, 1H), 7.68 (d, 1H, *J* = 7.8), 7.51 (ddd, 1H, *J* = 9.5, 7.8, 2.3), 7.35 (d, 1H, *J* = 7.8), 7.19 (t, 1H, *J* = 7.8), 7.11 (t, 1H, *J* = 7.8), 7.07 - 6.90 (m, 3H), 7.01 (s, 1H), 6.22 (br s, 1H), 5.23 (s, 1H), 3.89 (t, 2H, *J* = 7.8), 3.57 - 3.49 (m, 4H), 3.15 (s, 3H), 3.07 (t, 2H, *J* = 7.8), 1.68 - 1.53 (m, 6H); ESI-MS *m/z* 463 (MH<sup>+</sup>).

Example 16: N<sup>4</sup>-(3-CHLORO-4-METHYLPHENYL)-N<sup>2</sup>-[2-(1H-INDOL-3-YL)ETHYL]-N<sup>2</sup>-METHYL-6-(1-PIPERIDINYL)-2,4-

PYRIMIDINEDIAMINE: Prepared by Procedures D, E (160°C, 12 hours, for substitution with *N*-methyltryptamine), and G. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.96 (br s, 1H), 7.69 (d, 1H, *J* = 7.5), 7.51 (s, 1H), 7.36 (d, 1H, *J* = 7.8), 7.19 (t, 1H, *J* = 7.8), 7.14 - 7.06 (m, 3H), 7.01 (s, 1H), 6.18 (br s, 1H), 5.29 (s, 1H), 3.89 (t, 2H, *J* = 7.8), 3.53 - 3.48 (m, 4H), 3.13 (s, 3H), 3.07 (t, 2H, *J* = 7.8), 2.31 (s, 3H),

1.70 - 1.55 (m, 6H); ESI-MS  $m/z$  475 ( $MH^+$ ).

Example 17:  $N^2$ -[2-(1H-INDOL-3-YL)ETHYL]- $N^4$ -(3-METHOXYPHENYL)- $N^2$ -METHYL-6-(1-PIPERIDINYL)-2,4-

5 PYRIMIDINEDIAMINE: Prepared by Procedures D, E (160°C, 12 hours, for substitution with *N*-methyltryptamine), and G.  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  8.02 (br s, 1H), 7.71 (d, 1H,  $J$  = 7.8), 7.34 (d, 1H,  $J$  = 8.3), 7.25 - 7.04 (m, 4H), 7.01 (s, 1H), 6.89 (d, 1H,  $J$  = 7.8), 6.57 (dd, 1H,  $J$  = 8.3, 2.4), 6.30 (br s, 1H), 5.42 (s, 1H), 3.91 (t, 2H,  $J$  = 7.7), 3.76 (s, 3H), 3.57 - 3.49 (m, 4H), 3.16 (s, 3H), 10 3.08 (t, 2H,  $J$  = 7.7), 1.70 - 1.53 (m, 6H); ESI-MS  $m/z$  457 ( $MH^+$ ).

15 Example 18:  $N^2$ -ETHYL- $N^2$ -[2-(1H-INDOL-3-YL)ETHYL]- $N^4$ -(4-METHYLPHENYL)-6-(1-PIPERIDINYL)-2,4-PYRIMIDINEDIAMINE:

Prepared by Procedures D, E (160°C, 12 hours, for substitution with *N*-ethyltryptamine), and G.  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  7.97 (br s, 1H), 7.71 (d, 1H,  $J$  = 7.8), 7.35 (d, 1H,  $J$  = 7.8), 7.25 - 7.16 (overlapping d at 7.23 & t at 7.22, 3H), 7.14 (t, 1H,  $J$  = 7.8), 7.08 (d, 2H,  $J$  = 7.8), 7.02 (s, 1H), 6.19 (br s, 1H), 5.34 (s, 1H), 3.82 (t, 2H,  $J$  = 7.9), 3.61 (q, 2H,  $J$  = 7.1), 3.55 - 3.45 (m, 4H), 3.08 (t, 2H,  $J$  = 7.9), 2.30 (s, 6H), 1.68 - 1.50 (m, 20 6H), 1.18 (t, 3H,  $J$  = 7.1); ESI-MS  $m/z$  455 ( $MH^+$ ).

Example 19:  $N^2$ -[2-(1H-INDOL-3-YL)ETHYL]- $N^2$ -(2-METHOXYETHYL)- $N^4$ -(4-METHYLPHENYL)-6-(1-PIPERIDINYL)-2,4-

30 PYRIMIDINEDIAMINE: Prepared by Procedures D, E (160°C, 12 hours, for substitution with *N*-methoxyethyltryptamine), and G.  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  7.96 (br s, 1H), 7.72 (d, 1H,  $J$  = 7.5), 7.35 (d, 1H,  $J$  = 7.8), 7.27 - 7.07 (m, 6H),

7.02 (s, 1H), 6.19 (br s, 1H), 5.35 (s, 1H), 3.88 (dd, 2H,  $J = 9.9, 5.4$ ), 3.74 (t, 2H,  $J = 6.0$ ), 3.60 (dd, 2H,  $J = 10.5, 4.8$ ), 3.57 - 3.46 (m, 4H), 3.34 (s, 3H), 3.12 - 3.07 (m, 2H), 2.32 (s, 6H), 1.70 - 1.58 (m, 6H); ESI-MS  $m/z$  485 ( $MH^+$ ).

Example 20:  $N^2$ -[2-(1H-3-INDOLYL)-1-METHYLETHYL]- $N^4$ -(4-METHYLPHENYL)-6-(1-PIPERIDINYL)-2,4-PYRIMIDINEDIAMINE:

Prepared by Procedures D, J, and G.  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  8.10 (br s, 1H) 7.70 (d, 1H,  $J = 7.8$ ), 7.36 (d, 1H,  $J = 8.1$ ), 7.19 - 6.98 (m, 7H), 6.60 (br s, 1H), 5.35 (s, 1H), 4.39 (br s, 1H), 4.44 - 4.36 (m, 1H), 3.55 - 3.45 (m, 4H), 3.14 (dd 1H,  $J = 14.1, 5.1$ ), 2.84 (dd, 1H,  $J = 14.1, 7.5$ ), 2.33 (s, 3H), 1.62 - 1.50 (m, 6H), 1.18 (d, 3H,  $J = 6.6$ ); ESI-MS  $m/z$  441 ( $MH^+$ ).

Example 21:  $N^2$ -[2-(1H-INDOL-3-YL)-1-METHYLETHYL]- $N^2$ -METHYL- $N^4$ -(4-METHYLPHENYL)-6-(1-PIPERIDINYL)-2,4-PYRIMIDINEDIAMINE:

Prepared by Procedures D, E (160°C, 12 hours, for substitution with  $N, \alpha$ -dimethyltryptamine), and G.  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  7.92 (br s, 1H) 7.73 (d, 1H,  $J = 7.8$ ), 7.34 (d, 1H,  $J = 7.8$ ), 7.19 - 7.09 (m, 6H), 7.03 (s, 1H), 6.17 (br s, 1H), 5.34 (s, 1H), 3.51 - 3.44 (m, 5H), 3.11 - 3.05 (m, 1H), 3.02 (s, 2H), 2.90 (dd, 1H,  $J = 14.7, 7.5$ ), 2.32 (s, 3H), 1.65 - 1.49 (m, 6H), 1.18 (d, 3H,  $J = 6.6$ ); ESI-MS  $m/z$  455 ( $MH^+$ ).

Example 22:  $N^2$ -METHYL- $N^4$ -(4-METHYLPHENYL)- $N^2$ -PHENETHYL-6-(1-PIPERIDINYL)-2,4-PYRIMIDINEDIAMINE:

Prepared by Procedures D, E (160°C, 12 hours, for substitution at C2 of the pyrimidine), and G. ESI-MS  $m/z$  402 ( $MH^+$ ).

Example 23: 2-(4-BENZYL-1-PIPERAZINYL)-N-(4-METHYLPHENYL)-6-(1-PIPERIDINYL)-4-PYRIMIDINAMINE:

Prepared by Procedures D, I (140°C, overnight, for substitution with *N*-benzylpiperazine), and F (2 hours).

5 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.38 - 7.26 (m, 5H) 7.18 (d, 1H, *J* = 7.8), 7.12 (d, 1H, *J* = 7.8), 6.18 (br s, 1H), 5.34 (s, 1H), 3.93 - 3.87 (m, 4H), 3.77 (t, 4H, *J* = 5.0), 3.55 (s, 2H), 3.48 - 3.42 (m, 4H), 2.49 (t, 4H, *J* = 5.0), 2.31 (s, 3H), 1.66 - 1.49 (m, 6H); ESI-MS *m/z* 443 (MH<sup>+</sup>).

10

Example 24: N-(4-METHYLPHENYL)-2-(4-PHENYL-1-PIPERIDINYL)-6-(1-PIPERIDINYL)-4-PYRIMIDINAMINE:

Prepared by Procedures D, E (16 hours, for substitution with 4-phenylpiperidine), and F (1 hour). <sup>1</sup>H NMR (300 MHz,

15 CDCl<sub>3</sub>) δ 7.34 - 7.24 (m, 5H), 7.19 (d, 2H, *J* = 7.8), 7.12 (d, 2H, *J* = 7.8), 6.22 (br s, 1H), 5.36 (s, 1H), 4.89 (d with fine splitting, 2H, *J* = 13.0), 3.52 - 3.42 (m, 4H), 2.86 (dt, 2H, *J* = 1.0, 13.0), 2.73 (tt, 1H, *J* = 11.6, 1.5), 2.32 (s, 3H), 1.89 (d with fine splitting, 2H, *J* = 12.0), 1.74 (ddd, 2H, *J* = 13.0, 12.0, 1.5), 1.67 - 1.52 (m, 6H); ESI-MS *m/z* 428 (MH<sup>+</sup>).

20

Example 25: N-(4-METHYLPHENYL)-2-(4-PHENYLPIPERAZINYL)-6-(1-PIPERIDINYL)-4-PYRIMIDINAMINE:

Prepared by Procedures D, G (180°C, 2.5 hours, for substitution with *N*-phenylpiperazine), and G (140°C, overnight). <sup>1</sup>H NMR (300

25 MHz, CDCl<sub>3</sub>) δ 7.28 (t, 2H, *J* = 7.8), 7.19 (d, 2H, *J* = 7.8), 7.13 (d, 2H, *J* = 7.8), 6.99 (d, 2H, *J* = 7.8), 6.89 (t, 1H, *J* = 7.8), 6.23 (br s, 1H), 5.38 (s, 1H), 3.91 (t, 2H, *J* = 4.6), 3.54 - 3.44 (m, 4H), 3.23 (t, 2H, *J* = 4.6), 2.34 (s, 3H), 1.71 - 1.51 (m, 6H); ESI-MS *m/z* 429 (MH<sup>+</sup>).

30



Example 26: 2-[4-(2-ETHYLPHENYL)-1-PIPERAZINYL]-N-(4-METHYLPHENYL)-6-(1-PIPERIDINYL)-4-PYRIMIDINAMINE:

Prepared by Procedures D, E (120°C), and F. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.28 (d, 1H, *J* = 7.8), 7.24 - 7.08 (m, 7H), 6.37 (br s, 1H), 5.41 (s, 1H), 3.98 - 3.90 (m, 4H), 3.53 - 3.47 (m, 4H), 2.99 - 2.92 (m, 4H), 2.80 (q, 2H, *J* = 8.3), 2.35 (s, 3H), 1.69 - 1.54 (m, 6H), 1.31 (t, 3H, *J* = 8.3); ESI-MS *m/z* 457 (MH<sup>+</sup>).

Example 27: 2-[4-(2,6-DIMETHYLPHENYL)-1-PIPERAZINYL]-N-(4-METHYLPHENYL)-6-(1-PIPERIDINYL)-4-PYRIMIDINAMINE:

Prepared by Procedures D, E (120°C), and F. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.22 (d, 2H, *J* = 7.8), 7.15 (d, 2H, *J* = 7.8), 7.05 - 7.95 (m, 3H), 6.30 (br s, 1H), 5.39 (s, 1H), 3.88 (t, 4H, *J* = 4.6), 3.53 - 3.47 (m, 4H), 3.15 (t, 4H, *J* = 4.6), 2.37 (s, 6H), 2.34 (s, 3H), 1.68 - 1.53 (m, 6H); ESI-MS *m/z* 457 (MH<sup>+</sup>).

Example 28: N-{2-[4-(2,4-DIMETHOXYPHENYL)PIPERAZINYL]-6-(1-PIPERIDINYL)-4-PYRIMIDINYL}-N-(4-METHYLPHENYL)AMINE:

Prepared by Procedures D, E (150°C, 16 hours), and F (5 hours). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.18 (d, 2H, *J* = 8.1), 7.12 (d, 2H, *J* = 8.1), 6.88 (d, 1H, *J* = 9.0), 6.50 (d, 1H, *J* = 2.4), 6.43 (dd, 1H, *J* = 8.7, 2.4), 6.23 (br s, 1H), 5.36 (s, 1H), 3.94 (t, 4H, *J* = 7.5), 3.87 (s, 3H), 3.79 (s, 3H), 3.52 - 3.44 (m, 4H), 3.03 (t, 4H, *J* = 7.5), 2.33 (s, 3H), 1.65 - 1.52 (m, 6H); ESI-MS *m/z* 488 (MH<sup>+</sup>).

Example 29: N-(4-METHYLPHENYL)-6-(1-PIPERIDINYL)-2-{4-[3-(TRIFLUOROMETHYL)PHENYL]-1-PIPERAZINYL}-4-PYRIMIDINAMINE:

Prepared by Procedures D, E (120°C, 16 hours), and F. <sup>1</sup>H

NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.36 (t, 1H,  $J$  = 7.8), 7.20 - 7.09 (m, 7H), 6.25 (br s, 1H), 5.37 (s, 1H), 4.93 (t, 4H,  $J$  = 4.6), 3.52 - 3.45 (m, 4H), 3.26 (t, 4H,  $J$  = 4.6), 2.34 (s, 3H), 1.66 - 1.52 (m, 6H); ESI-MS  $m/z$  497 (MH<sup>+</sup>).

5

Example 30: N-(4-METHYLPHENYL)-6-(1-PIPERIDINYL)-2-[4-(2-PYRIDYL)-1-PIPERAZINYL]-4-PYRIMIDINAMINE: Prepared by Procedures D, G (120°C, 12 hours, for substitution with *N*-pyrid-2-ylpiperazine), and G (140°C). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  8.22 (dd, 1H,  $J$  = 4.4, 1.5), 7.50 (dd, 1H,  $J$  = 7.8, 1.5), 7.20 (d, 2H,  $J$  = 8.1), 7.13 (d, 2H,  $J$  = 8.1), 6.69 (d, 1H,  $J$  = 7.8), 6.63 (t, 1H,  $J$  = 7.8), 6.26 (br s, 1H), 5.38 (s, 1H), 3.89 (t, 4H,  $J$  = 4.8), 3.62 (t, 4H,  $J$  = 4.8), 3.55 - 3.45 (m, 4H), 2.33 (s, 3H), 1.70 - 1.52 (m, 6H); ESI-MS  $m/z$  430 (MH<sup>+</sup>).

15

Example 31: N-(4-METHYLPHENYL)-2-[4-(3-METHYL-2-PYRIDINYL)-1-PIPERAZINYL]-6-(1-PIPERIDINYL)-4-PYRIMIDINAMINE: Prepared from 2-(4-benzyl-1-piperazinyl)-*N*-(4-methylphenyl)-6-(1-piperidinyl)-4-pyrimidinamine by Procedures K and L. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  8.19 (dd, 1H,  $J$  = 4.4, 2.2), 7.42 (dd, 1H,  $J$  = 7.8, 2.2), 7.19 (d, 2H,  $J$  = 8.1), 7.12 (d, 2H,  $J$  = 8.1), 6.85 (dd, 1H,  $J$  = 7.8, 4.4), 6.20 (br s, 1H), 5.38 (s, 1H), 3.93 - 3.87 (m, 4H), 3.53 - 3.48 (m, 4H), 3.24 - 3.18 (m, 4H), 2.33 (s, 3H), 1.67 - 1.53 (m, 6H); ESI-MS  $m/z$  444 (MH<sup>+</sup>).

20

25

Example 32: N-(4-METHYLPHENYL)-6-(1-PIPERIDINYL)-2-{4-[4-(TRIFLUOROMETHYL)-2-PYRIDINYL]-1-PIPERAZINYL}-4-PYRIMIDINAMINE: Prepared by Procedures D, E (16 hours), and F. ESI-MS  $m/z$  498 (MH<sup>+</sup>).

30

Example 33: N-(4-METHYLPHENYL)-6-(1-PIPERIDINYL)-2-{4-[6-(TRIFLUOROMETHYL)-2-PYRIDINYL]-1-PIPERAZINYL}-4-

PYRIMIDINAMINE: Prepared by Procedures D, E (16 hours), and F.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.56 (d, 1H,  $J = 8.1$ ), 7.19 (d, 2H,  $J = 8.4$ ), 7.14 (d, 2H,  $J = 8.4$ ), 6.94 (d, 1H,  $J = 7.2$ ), 6.80 (d, 1H,  $J = 8.7$ ), 6.23 (br s, 1H), 5.37 (s, 1H), 3.90 - 3.87 (m, 4H), 3.69 - 3.66 (m, 4H), 3.50 - 4.46 (m, 4H), 2.34 (s, 3H), 1.67 - 1.53 (m, 6H); ESI-MS  $m/z$  498 ( $\text{MH}^+$ ).

Example 34: N-(4-METHYLPHENYL)-6-(1-PIPERIDINYL)-2-{4-[3-(TRIFLUOROMETHYL)-2-PYRIDINYL]-1-PIPERAZINYL}-4-

PYRIMIDINAMINE: Prepared by Procedures D, E (16 hours), and F.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.43 (dd, 1H,  $J = 4.4$ , 2.2), 7.87 (dd, 1H,  $J = 7.8$ , 2.2), 7.19 (d, 2H,  $J = 8.1$ ), 7.13 (d, 2H,  $J = 8.1$ ), 6.99 (dd, 1H,  $J = 7.8$ , 4.4), 6.23 (br s, 1H), 5.37 (s, 1H), 3.89 (t, 4H,  $J = 4.8$ ), 3.53 - 3.48 (m, 4H), 3.36 (t, 4H,  $J = 4.8$ ), 2.33 (s, 3H), 1.67 - 1.53 (m, 6H); ESI-MS  $m/z$  498 ( $\text{MH}^+$ ).

Example 35: N-CYCLOHEXYL-6-(1-PIPERIDINYL)-2-{4-[3-(TRIFLUOROMETHYL)-2-PYRIDINYL]-1-PIPERAZINYL}-4-

PYRIMIDINAMINE: Prepared by Procedures M, E (120°C, for addition of piperidine), and F (3 hours).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.43 (d, 1H,  $J = 5.6$ ), 7.84 (d, 1H,  $J = 7.4$ ), 6.95 (dd, 1H,  $J = 7.4$ , 5.6), 4.95 (s, 1H), 4.34 (br s, 1H), 3.84 (t, 4H,  $J = 5.1$ ), 3.55 - 3.38 (m, 5H), 3.34 (t, 4H,  $J = 5.1$ ), 2.02 (dd, 2H,  $J = 12.0$ , 1.4), 1.79 - 1.71 (m, 2H), 1.69 - 1.52 (m, 6H), 1.44 - 1.10 (m, 6H); ESI-MS  $m/z$  490 ( $\text{MH}^+$ ).

Example 36: N-BICYCLO[2.2.1]HEPT-2-YL-6-(1-PIPERIDINYL)-

2-{4-[3-(TRIFLUOROMETHYL)-2-PYRIDINYL]-1-PIPERAZINYL}-4-

PYRIMIDINAMINE: Prepared by Procedures M, E (120°C, for addition of piperidine), and F (3 hours). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.42 (d, 1H, *J* = 5.6), 7.86 (d, 1H, *J* = 7.4), 6.95 (dd, 1H, *J* = 7.4, 5.6), 4.95 (s, 1H), 4.37 (br s, 1H), 3.84 (t, 4H, *J* = 5.1), 3.57 - 3.47 (m, 4H), 3.40 - 3.31 (m, 5H), 2.25 (br s, 2H), 1.78 (ddd, 2H, *J* = 13.0, 4.6, 1.4), 1.67 - 1.42 (m, 9H), 1.25 - 1.12 (m, 4H); ESI-MS *m/z* 502 (MH<sup>+</sup>).

Example 37: N-(4-METHYLPHENYL)-6-(1-PIPERIDINYL)-2-[4-(2-PYRIMIDINYL)-1-PIPERAZINYL]-4-PYRIMIDINAMINE: Prepared by

Procedures D, G (120°C, 12 hours, for substitution with *N*-pyrimid-2-ylpiperazine), and G (150°C, 24 hours). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.33 (d, 2H, *J* = 4.9), 7.19 (d, 2H, *J* = 7.8), 7.13 (d, 2H, *J* = 7.8), 6.50 (t, 1H, *J* = 7.8), 6.23 (br s, 1H), 5.37 (s, 1H), 3.97 - 3.82 (m, 8H), 3.56 - 3.44 (m, 4H), 2.34 (s, 3H), 1.70 - 1.53 (m, 6H); ESI-MS *m/z* 431 (MH<sup>+</sup>).

Example 38: N-(4-METHYLPHENYL)-6-(1-PIPERIDINYL)-2-(1-PYRROLIDINYL)-4-PYRIMIDINAMINE: Prepared by Procedures D,

G (120°C, 3 hours, for substitution with pyrrolidine), and G (140°C, 12 hours). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.20 (d, 2H, *J* = 7.8), 7.11 (d, 2H, *J* = 7.8), 6.39 (br s, 1H), 5.34 (s, 1H), 3.56 (t, 4H, *J* = 5.6), 3.53 - 3.44 (m, 4H), 2.33 (s, 3H), 1.91 (quintet, 4H, *J* = 5.6), 1.67 - 1.50 (m, 6H); ESI-MS *m/z* 338 (MH<sup>+</sup>).

Example 39: N-[2-(2,3-DIHYDRO-1H-INDOL-1-YL)-6-(1-PIPERIDINYL)-4-PYRIMIDINYL]-N-(4-METHYLPHENYL)AMINE:

Prepared by Procedures D, E (16 hours), and F. <sup>1</sup>H NMR

(300 MHz, CDCl<sub>3</sub>)  $\delta$  8.31 (d, 1H,  $J$  = 7.8), 7.28 - 7.15 (m, 6H), 6.86 (t, 1H,  $J$  = 7.8), 6.31 (br s, 1H), 5.49 (s, 1H), 4.22 (t, 4H,  $J$  = 8.3), 3.59 - 3.53 (m, 4H), 3.13 (t, 4H,  $J$  = 8.3), 2.35 (s, 3H), 1.70 - 1.55 (m, 6H); ESI-MS  $m/z$  386 (MH<sup>+</sup>).

Example 40: N-(4-METHYLPHENYL)-N-[6-(1-PIPERIDINYL)-2-(1,2,3,4-TETRAHYDRO-1-QUINOLINYL)-4-PYRIMIDINYL]AMINE:

Prepared by Procedures D, G (180°C, 3 hours, for substitution with 1,2,3,4-tetrahydroquinoline), and G (140°C, 12 hours). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.87 (d, 1H,  $J$  = 7.8), 7.19 (d, 2H,  $J$  = 7.8), 7.15 - 7.07 (m, 4H), 6.93 (t, 1H,  $J$  = 7.8), 6.33 (br s, 1H), 5.49 (s, 1H), 4.04 (t, 2H,  $J$  = 6.0), 3.54 - 3.44 (m, 4H), 2.79 (t, 2H,  $J$  = 6.0), 2.34 (s, 3H), 1.98 (pentet, 2H,  $J$  = 6.0), 1.69 - 1.52 (m, 6H); ESI-MS  $m/z$  400 (MH<sup>+</sup>).

Example 41: N-(4-METHYLPHENYL)-N-[6-(1-PIPERIDINYL)-2-(1,2,3,4-TETRAHYDRO-2-ISOQUINOLINYL)-4-PYRIMIDINYL]AMINE:

Prepared by Procedures D, G (180°C, 3 hours, for substitution with 1,2,3,4-tetrahydroisoquinoline), and G (140°C, 12 hours). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.56 (d, 1H,  $J$  = 7.8), 7.26 - 7.06 (m, 7H), 6.37 (br s, 1H), 5.35 (s, 1H), 4.89 (s, 2H), 4.00 (t, 2H,  $J$  = 6.0), 3.58 - 3.44 (m, 4H), 2.91 (t, 2H,  $J$  = 6.0), 2.32 (s, 3H), 1.68 - 1.47 (m, 6H); ESI-MS  $m/z$  400 (MH<sup>+</sup>).

Example 42: N-[2-(6,7-DIMETHOXY-3,4-DIHYDRO-2(1H)-ISOQUINOLINYL)-6-(1-PIPERIDINYL)-4-PYRIMIDINYL]-N-(4-

METHYLPHENYL)AMINE: Prepared by Procedures D, E (160°C, 12 hours), and F (5 hours). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.19 (d, 2H,  $J$  = 7.8), 7.13 (d, 2H,  $J$  = 7.8), 6.70 (s,

1H), 6.64 (s, 1H), 6.25 (br s, 1H), 5.36 (s, 1H), 4.82 (s, 2H), 4.01 (t, 2H,  $J = 5.9$ ), 3.89 (s, 3H), 3.87 (s, 3H), 3.58 - 3.44 (m, 4H), 2.84 (t, 2H,  $J = 5.9$ ), 2.33 (s, 3H), 1.68 - 1.52 (m, 6H); ESI-MS  $m/z$  460 ( $MH^+$ ).

5

Example 43: N-[2-(2,3-DIHYDRO-1H-BENZO[DE]ISOQUINOLIN-2-YL)-6-(1-PIPERIDINYL)-4-PYRIMIDINYL]-N-(4-METHYLPHENYL)AMINE: Prepared by Procedures D, E (160°C, 12 hours), and G. ESI-MS  $m/z$  436 ( $MH^+$ ).

10

Example 44: 4-PHENYL-1-[4-(1-PIPERIDINYL)-6-(4-TOLUIDINO)-2-PYRIMIDINYL]-4-PIPERIDINOL: Prepared by Procedures D, E (23 hours), and F.  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  7.51 (d, 2H,  $J = 7.5$ ), 7.36 (t, 2H,  $J = 7.8$ ), 7.26 (t, 1H +  $CHCl_3$ ,  $J = 7.8$ ), 7.19 (d, 2H,  $J = 8.4$ ), 7.12 (d, 2H,  $J = 8.4$ ), 6.20 (br s, 1H), 5.36 (s, 1H), 4.67 (br d, 2H,  $J = 13.5$ ), 3.50 - 3.45 (m, 4H), 4.67 (br t, 2H,  $J = 13.1$ ), 2.33 (s, 3H), 2.10 (dt, 2H,  $J = 4.2, 12.6$ ), 1.78 (br d, 2H,  $J = 13.5$ ), 1.65 - 1.53 (m, 6H); ESI-MS  $m/z$  444 ( $MH^+$ ).

20

Example 45:  $N^2, N^2$ -BIS(2-METHOXYETHYL)- $N^4$ -(4-METHYLPHENYL)-6-(1-PIPERIDINYL)-2,4-PYRIMIDINEDIAMINE: Prepared by Procedures D, G [140°C, 2 hours, for substitution with bis(methoxyethyl)amine], and G (140 °C, 1.5 hours).  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  7.20 (d, 2H,  $J = 7.8$ ), 7.10 (d, 2H,  $J = 7.8$ ), 6.20 (br s, 1H), 5.33 (s, 1H), 3.77 (t, 4H,  $J = 6.2$ ), 3.59 (t, 4H,  $J = 6.3$ ), 3.47 - 3.40 (m, 4H), 3.36 (s, 6H), 1.64 - 1.49 (m, 6H); ESI-MS  $m/z$  400 ( $MH^+$ ).

30

Example 46: N-(4-METHYLPHENYL)-2-(3-PHENYL-4-MORPHOLINYL)-6-(1-PIPERIDINYL)-4-PYRIMIDINAMINE: Prepared

by Procedures D, E (16 hours), and F (1 hour).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )

5  $\delta$  7.51 (d, 2H,  $J = 7.8$ ), 7.31 (t, 2H,  $J = 7.8$ ), 7.23 (t, 1H,  $J = 7.8$ ), 7.15 (d, 2H,  $J = 7.8$ ), 7.10 (d, 2H,  $J = 7.8$ ), 6.22 (br s, 1H), 5.84 (d, 1H,  $J = 1.0$ ), 5.36 (s, 1H), 4.51 - 4.42 (m, 2H), 3.94 (m, 2H), 3.66 (dt, 1H,  $J = 1.0$ , 11.5), 3.49 - 3.43 (m, 4H), 3.24 (dt, 1H,  $J = 1.5$ , 11.5), 2.32 (s, 3H), 1.64 - 1.47 (m, 6H); ESI-MS  $m/z$  430 ( $\text{MH}^+$ ).

10

Example 47: *N*-(4-METHYLPHENYL)-2-(2-PHENYL-4-MORPHOLINYL)-6-(1-PIPERIDINYL)-4-PYRIMIDINAMINE: Prepared by Procedures D, E (14 hours), and F (100°C, 2 hours).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.46 (d, 2H,  $J = 7.8$ ), 7.38 (t, 2H,  $J = 7.8$ ), 7.34 (t, 1H,  $J = 7.8$ ), 7.18 (d, 2H,  $J = 8.7$ ), 7.13 (d, 2H,  $J = 8.4$ ), 6.19 (br s, 1H), 5.38 (s, 1H), 4.70 (br d, 1H,  $J = 12.6$ ), 4.58 - 4.51 (m, 1H), 4.11 (dd, 1H,  $J = 10.2$ , 2.4), 3.80 (dt, 1H,  $J = 2.7$ , 11.7), 3.50 - 3.43 (m, 4H), 3.10 (dt, 1H,  $J = 2.1$ , 12.8), 2.89 (dd, 1H,  $J = 13.2$ , 10.2), 2.33 (s, 3H), 1.66 - 1.50 (m, 6H); ESI-MS  $m/z$  430 ( $\text{MH}^+$ ).

15

20

Example 48: *N*-(4-METHYLPHENYL)-2-[(2*S*,3*R*)-3-METHYL-2-PHENYLMORPHOLINYL]-6-(1-PIPERIDINYL)-4-PYRIMIDINAMINE:

25 Prepared by Procedures D, E (120°C), and F (1 hour).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.42 (d, 2H,  $J = 7.8$ ), 7.39 (t, 2H,  $J = 7.8$ ), 7.27 (t, 1H,  $J = 7.8$ ), 7.20 (d, 2H,  $J = 7.8$ ), 7.14 (d, 2H,  $J = 7.8$ ), 6.25 (br s, 1H), 5.39 (s, 1H), 4.99 - 4.90 (m, 1H), 4.77 (d, 1H,  $J = 1.5$ ), 4.39 (dd, 1H,  $J = 13.0$ , 1.5), 4.15 (dd, 1H,  $J = 8.3$ , 1.5), 3.80 (dt, 1H,  $J = 3.7$ , 11.6), 3.53 - 3.45 (m, 4H), 3.26 (dt, 1H,  $J = 3.7$ , 13.0), 2.33 (s, 3H), 1.68 - 1.52 (m, 6H), 0.90 (d,

30

3H,  $J = 8.3$ ); ESI-MS  $m/z$  444 ( $MH^+$ ).

Example 49: 2-[(2R,3R)-3-(METHOXYMETHYL)-2-PHENYLMORPHOLINYL]-N-(4-METHYLPHENYL)-6-(1-PIPERIDINYL)-

5 4-PYRIMIDINAMINE: Prepared by Procedures D, E, and F (3 hours).  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  7.56 (d, 2H,  $J = 7.8$ ), 7.31 (t, 2H,  $J = 7.8$ ), 7.27 - 7.20 (m, 3H), 7.13 (d, 2H,  $J = 7.8$ ), 6.31 (br s, 1H), 5.84 (d, 1H,  $J = 1.0$ ), 5.35 (dd, 1H,  $J = 9.3, 2.7$ ), 5.11 (s, 1H), 4.28 (d with  
10 splitting, 1H,  $J = 13.0$ ), 4.01 (t, 1H,  $J = 9.0$ ), 3.58 - 3.46 (m, 6H), 3.40 (s, 3H), 3.27 - 3.15 (m, 1H), 2.31 (s, 3H), 1.69 - 1.50 (m, 6H); ESI-MS  $m/z$  473 ( $MH^+$ ).

Example 50:  $N^4, N^4$ -DIMETHYL- $N^2, N^6$ -DIPHENYL-2,4,6-

15 PYRIMIDINETRIAMINE: Prepared by Procedures A, C, and G (140°C, overnight).  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  7.68 (d, 2H,  $J = 7.8$ ), 7.38 - 7.27 (m, 6H), 7.11 - 7.04 (m, 1H), 6.95 (t, 1H,  $J = 7.8$ ), 6.75 (br s, 1H), 6.38 (br s, 1H), 5.45 (s, 1H), 3.06 (s, 6H); ESI-MS  $m/z$  306 ( $MH^+$ ).

20 Example 51:  $N^4, N^4$ -DIMETHYL- $N^6$ -(2-METHYLPHENYL)- $N^2$ -PHENYL-

2,4,6-PYRIMIDINETRIAMINE: Prepared by Procedures A, C, and G (140°C, overnight).  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  7.63 (d, 2H,  $J = 7.5$ ), 7.43 (d, 1H,  $J = 7.5$ ), 7.31 - 7.24 (m, 3H), 7.21 (d, 1H,  $J = 7.8$ ), 7.11 (t, 1H,  $J = 7.4$ ), 6.96 (t, 1H,  $J = 7.7$ ), 6.73 (br s, 1H), 6.12 (br s, 1H), 5.16 (s, 1H), 3.01 (s, 6H), 2.29 (s, 3H); ESI-MS  $m/z$  320 ( $MH^+$ ).

30 Example 52:  $N^4, N^4$ -DIMETHYL- $N^6$ -(3-METHYLPHENYL)- $N^2$ -PHENYL-

2,4,6-PYRIMIDINETRIAMINE: Prepared by Procedures A, C, and G (140°C, overnight).  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  7.63



(d, 2H,  $J = 7.8$ ), 7.29 (t, 2H,  $J = 7.8$ ), 7.21 (d, 1H,  $J = 8.1$ ), 7.16 - 7.11 (m, 2H), 6.97 (d, 1H,  $J = 8.1$ ), 6.91 (d, 1H,  $J = 7.5$ ), 6.78 (br s, 1H), 6.38 (br s, 1H), 5.44 (s, 1H), 3.05 (s, 6H), 2.35 (s, 3H); ESI-MS  $m/z$  320 (MH<sup>+</sup>).

Example 53:  $N^4, N^4$ -DIMETHYL- $N^6$ -(3-METHYLPHENYL)- $N^2$ -(4-METHYLPHENYL)-2,4,6-PYRIMIDINETRIAMINE: Prepared by Procedures A, C, and G (overnight). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.50 (d, 2H,  $J = 7.8$ ), 7.25 - 7.08 (m, 5H), 6.90 (d, 1H,  $J = 7.5$ ), 6.86 (br s, 1H), 6.54 (br s, 1H), 5.44 (s, 1H), 3.05 (s, 6H), 2.34 (s, 3H), 2.31 (s, 3H); ESI-MS  $m/z$  334 (MH<sup>+</sup>).

Example 54:  $N^4, N^4$ -DIMETHYL- $N^6$ -(4-METHYLPHENYL)- $N^2$ -PHENYL-2,4,6-PYRIMIDINETRIAMINE: Prepared by Procedures A, C, and G (140°C, overnight). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.63 (d, 2H,  $J = 7.8$ ), 7.28 (t, 2H,  $J = 7.5$ ), 7.21 (d, 2H,  $J = 7.8$ ), 7.15 (d, 2H,  $J = 8.1$ ), 6.96 (t, 1H,  $J = 7.5$ ), 6.71 (br s, 1H), 6.29 (br s, 1H), 5.39 (s, 1H), 3.04 (s, 6H), 2.34 (s, 3H); ESI-MS  $m/z$  320 (MH<sup>+</sup>).

Example 55:  $N^2$ -(3,4-DICHLOROPHENYL)- $N^4, N^4$ -DIMETHYL- $N^6$ -(4-METHYLPHENYL)-2,4,6-PYRIMIDINETRIAMINE: Prepared by Procedures B, C, and G (180°C, 3 hours). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  8.04 (d, 1H,  $J = 2.1$ ), 7.27 (d, 1H,  $J = 7.8$ ), 7.24 (dd, 1H,  $J = 7.8, 2.1$ ), 7.19 (d, 2H,  $J = 8.7$ ), 7.15 (d, 2H,  $J = 8.7$ ), 7.01 (br s, 1H), 6.59 (br s, 1H), 5.39 (s, 1H), 3.04 (s, 6H), 2.35 (s, 3H); ESI-MS  $m/z$  388 (MH<sup>+</sup> with <sup>35</sup>Cl, <sup>35</sup>Cl), 390 (MH<sup>+</sup> with <sup>35</sup>Cl, <sup>37</sup>Cl), 392 (MH<sup>+</sup> with <sup>37</sup>Cl, <sup>37</sup>Cl).

Example 56:  $N^4, N^4$ -DIMETHYL- $N^2, N^6$ -BIS(4-METHYLPHENYL)-2,4,6-PYRIMIDINETRIAMINE: Prepared by Procedures B, C, and G (180°C, 3 hours).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.49 (d, 2H,  $J = 8.7$ ), 7.19 (d, 2H,  $J = 8.4$ ), 7.14 (d, 2H,  $J = 8.4$ ), 7.08 (d, 2H,  $J = 8.4$ ), 6.73 (br s, 1H), 6.39 (br s, 1H), 5.37 (s, 1H), 3.02 (s, 6H); ESI-MS  $m/z$  334 ( $\text{MH}^+$ ).

Example 57:  $N^4$ -(3-FLUOROPHENYL)- $N^6, N^6$ -DIMETHYL- $N^2$ -PHENYL-2,4,6-PYRIMIDINETRIAMINE: Prepared by Procedures A, C, and G (140°C, overnight).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.62 (d, 2H,  $J = 7.8$ ), 7.34 - 7.23 (m, 5H), 7.01 (t, 1H,  $J = 7.4$ ), 6.77 (br s, 1H), 6.38 (br s, 1H), 5.43 (s, 1H), 3.07 (s, 6H); ESI-MS  $m/z$  324 ( $\text{MH}^+$ ).

Example 58:  $N^2$ -(4-CHLOROPHENYL)- $N^6, N^6$ -DIMETHYL- $N^2$ -PHENYL-2,4,6-PYRIMIDINETRIAMINE: Prepared by Procedures A, C, and G (150°C, overnight).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.60 (d, 2H,  $J = 7.5$ ), 7.32 - 7.26 (m, 6H), 6.96 (t, 1H,  $J = 7.5$ ), 6.77 (br s, 1H), 6.34 (br s, 1H), 5.34 (s, 1H), 3.04 (s, 6H); ESI-MS  $m/z$  340 ( $\text{MH}^+$  with  $^{35}\text{Cl}$ ), 342 ( $\text{MH}^+$  with  $^{37}\text{Cl}$ ).

Example 59:  $N^4$ -(4-BROMOPHENYL)- $N^6, N^6$ -DIMETHYL- $N^2$ -PHENYL-2,4,6-PYRIMIDINETRIAMINE: Prepared by Procedures A, C, and G (150°C, overnight).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.59 (d, 2H,  $J = 8.5$ ), 7.42 (d, 2H,  $J = 8.5$ ), 7.31 - 7.22 (m, 4H), 6.98 (t, 1H,  $J = 7.2$ ), 6.92 (br s, 1H), 6.48 (br s, 1H), 5.35 (s, 1H), 3.05 (s, 6H), ESI-MS  $m/z$  384 ( $\text{MH}^+$  with  $^{79}\text{Br}$ ), 386 ( $\text{MH}^+$  with  $^{81}\text{Br}$ ).

Example 60:  $N^4$ -(3,4-DICHLOROPHENYL)- $N^6, N^6$ -DIMETHYL- $N^2$ -PHENYL-2,4,6-PYRIMIDINETRIAMINE: Prepared by Procedures

A, C, and G (0.5mL diisopropylethylamine added, 150°C, overnight).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.61 (d with s at the center, 3H,  $J = 7.8$ ), 7.34 (d, 2H,  $J = 7.8$ ), 7.29 (d, 1H,  $J = 8.7$ ), 7.17 (dd, 1H,  $J = 8.7, 2.6$ ), 6.98 (t, 1H,  $J = 7.8$ ), 6.80 (br s, 1H), 6.33 (br s, 1H), 5.33 (s, 1H), 3.07 (s, 6H); ESI-MS  $m/z$  373 ( $\text{MH}^+$ ).

Example 61:  $N^4$ -(4-CHLORO-3-METHYLPHENYL)- $N^6, N^6$ -DIMETHYL- $N^2$ -PHENYL-2,4,6-PYRIMIDINETRIAMINE: Prepared by Procedures A, C, and G (150°C, 1 hour).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.61 (dd, 2H,  $J = 7.4, 0.9$ ), 7.30 - 7.25 (m, 3H), 7.19 (d, 1H,  $J = 2.4$ ), 7.12 (dd, 1H,  $J = 8.5, 2.4$ ), 6.97 (t, 1H,  $J = 7.4$ ), 6.88 (br s, 1H), 6.44 (br s, 1H), 5.35 (s, 1H), 3.05 (s, 6H), 2.35 (s, 3H); ESI-MS  $m/z$  454 ( $\text{MH}^+$  with  $^{35}\text{Cl}$ ), 456 ( $\text{MH}^+$  with  $^{37}\text{Cl}$ ).

Example 62:  $N^4$ -(3-CHLORO-4-METHYLPHENYL)- $N^6, N^6$ -DIMETHYL- $N^2$ -PHENYL-2,4,6-PYRIMIDINETRIAMINE: Prepared by Procedures A, C, and F (100°C, 3 hours).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.63 (d, 2H,  $J = 7.8$ ), 7.41 (d, 1H,  $J = 1.8$ ), 7.30 (t, 2H,  $J = 7.8$ ), 7.18 (d, 1H,  $J = 7.8$ ), 7.09 (dd, 1H,  $J = 7.8, 1.8$ ), 6.98 (t, 1H,  $J = 7.8$ ), 6.67 (br s, 2H), 5.35 (s, 1H), 3.07 (s, 6H), 2.37 (s, 3H); ESI-MS  $m/z$  454 ( $\text{MH}^+$  with  $^{35}\text{Cl}$ ), 456 ( $\text{MH}^+$  with  $^{37}\text{Cl}$ ).

Example 63:  $N^4$ -(4-tert-BUTYLPHENYL)- $N^6, N^6$ -DIMETHYL- $N^2$ -PHENYL-2,4,6-PYRIMIDINETRIAMINE: Prepared by Procedures A, C, and G (150°C, 5 hours).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.62 (d, 2H,  $J = 7.5$ ), 7.36 (d, 2H,  $J = 8.7$ ), 7.29 (d, 2H,  $J = 7.5$ ), 7.25 (t, 2H,  $J = 8.7$ ), 6.95 (t, 1H,  $J = 7.4$ ), 6.69 (br s, 1H), 6.30 (br s, 1H), 5.44 (s, 1H), 3.05 (s, 6H), 1.33 (s, 9H); ESI-MS  $m/z$  362 ( $\text{MH}^+$ ).

Example 64:  $N^4, N^4$ -DIMETHYL- $N^6$ -(4-PHENOXYPHENYL)- $N^2$ -PHENYL-2,4,6-PYRIMIDINETRIAMINE: Prepared by Procedures A, C, and G (150°C, 2 hours).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.61 (d, 2H,  $J = 7.8$ ), 7.35 (t, 2H,  $J = 7.8$ ), 7.31 - 7.24 (m, 3H), 7.12 (t, 2H,  $J = 7.8$ ), 7.08 - 7.04 (m, 3H), 6.98 (t, 1H,  $J = 8.1$ ), 6.74 (br s, 1H), 6.71 (dd, 1H,  $J = 7.8$ , 2.0), 6.43 (br s, 1H), 5.41 (s, 1H), 3.03 (s, 6H); ESI-MS  $m/z$  398 ( $\text{MH}^+$ ).

Example 65:  $N^4, N^4$ -DIMETHYL- $N^6$ -(2-NAPHTHYL)- $N^2$ -PHENYL-2,4,6-PYRIMIDINETRIAMINE: Prepared by Procedures A, C, and G (150°C, 2 hours).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.81 (s, 1H), 7.80 (d, 1H,  $J = 7.5$ ), 7.75 (d, 2H,  $J = 7.8$ ), 7.65 (d, 2H,  $J = 7.5$ ), 7.49 - 7.37 (m, 3H), 7.29 (t, 2H,  $J = 7.5$ ), 6.98 (t, 1H,  $J = 8.1$ ), 6.85 (br s, 1H), 6.59 (br s, 1H), 5.51 (s, 1H), 3.06 (s, 6H); ESI-MS  $m/z$  356 ( $\text{MH}^+$ ).

Example 66:  $N^4$ -CYCLOHEXYL- $N^6, N^6$ -DIMETHYL- $N^2$ -PHENYL-2,4,6-PYRIMIDINETRIAMINE: Prepared by Procedures A, C, and G (140°C, 2 days).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.62 (d, 2H,  $J = 8.1$ ), 7.26 (t, 2H,  $J = 8.1$ ), 6.92 (t, 1H,  $J = 8.1$ ), 6.64 (br s, 1H), 4.96 (s, 1H), 4.39 (br d, 1H,  $J = 8.1$ ), 3.53 - 3.44 (m, 1H), 3.05 (s, 6H), 2.09 - 1.99 (m, 2H), 1.80 - 1.55 (m, 4H), 1.44 - 1.11 (m, 4H); ESI-MS  $m/z$  312 ( $\text{MH}^+$ ).

Example 67:  $N^4, N^4$ -DIMETHYL- $N^6$ -(4-METHYLCYCLOHEXYL)- $N^2$ -PHENYL-2,4,6-PYRIMIDINETRIAMINE: Prepared by Procedures A, C, and G (150°C, overnight). ESI-MS  $m/z$  326 ( $\text{MH}^+$ ).

Example 68:  $N^4$ -(4-*tert*-BUTYLCYCLOHEXYL)- $N^6, N^6$ -DIMETHYL- $N^2$ -

PHENYL-2,4,6-PYRIMIDINETRIAMINE: Prepared by Procedures A, C, and G (150°C, overnight).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.62 (d, 2H,  $J = 8.4$ ), 7.26 (t, 2H,  $J = 7.7$ ), 6.92 (t, 1H,  $J = 7.1$ ), 6.61 (br s, 1H), 4.96 (s, 1H), 4.32 (br d, 1H,  $J = 8.4$ ), 3.46 - 3.37 (m, 1H), 3.06 (s, 6H), 1.88 - 1.80 (m, 2H), 1.29 - 1.20 (m, 1H), 1.19 - 0.97 (m, 4H), 0.87 (s, 9H); ESI-MS  $m/z$  368 ( $\text{MH}^+$ ).

Example 69:  $N^4$ -BICYCLO[2.2.1]HEPT-2-YL- $N^6$ , $N^6$ -DIMETHYL- $N^2$ -PHENYL-2,4,6-PYRIMIDINETRIAMINE: Prepared by Procedures A, C, and G (140°C).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.62 (d, 2H,  $J = 7.8$ ), 7.26 (t, 2H,  $J = 8.0$ ), 6.92 (t, 1H,  $J = 7.2$ ), 6.62 (br s, 1H), 4.94 (s, 1H), 4.42 (br d, 1H,  $J = 5.4$ ), 3.45 - 3.37 (m, 1H), 3.06 (s, 6H), 2.33 - 2.27 (m, 1H), 1.82 (dd, 1H,  $J = 12.3, 6.0$ ), 1.56 - 1.42 (m, 2H), 1.30 - 1.14 (m, 5H), 0.91 - 0.85 (m, 1H); ESI-MS  $m/z$  324 ( $\text{MH}^+$ ).

Example 70:  $N^4$ , $N^4$ -DIMETHYL- $N^2$ -PHENYL- $N^6$ -(1,7,7-TRIMETHYLBICYCLO[2.2.1]HEPT-2-YL)-2,4,6-PYRIMIDINETRIAMINE: Prepared by Procedures A, C, and G (overnight).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.62 (d, 2H,  $J = 7.8$ ), 7.26 (t, 2H,  $J = 7.8$ ), 6.93 (t, 1H,  $J = 7.7$ ), 6.87 (br s, 1H), 4.95 (s, 1H), 4.80 (br d, 1H,  $J = 6.9$ ), 3.94 - 3.84 (m, 1H), 3.06 (s, 6H), 2.45 - 2.34 (m, 1H), 1.82 - 1.62 (m, 3H), 1.46 - 1.32 (m, 1H), 1.29 - 1.16 (m, 2H), 0.99 (s, 3H), 0.90 (s, 3H), 0.89 (s, 3H); ESI-MS  $m/z$  366 ( $\text{MH}^+$ ).

Example 71:  $N^4$ , $N^4$ -DIMETHYL- $N^2$ -PHENYL- $N^6$ -[(2R,3S)-3,6,6-TRIMETHYLBICYCLO[3.1.1]HEPT-2-YL]-2,4,6-PYRIMIDINETRIAMINE: Prepared by Procedures A, C, and G (5

hours).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.64 (d, 2H,  $J = 8.1$ ), 7.26 (t, 2H,  $J = 8.1$ ), 6.92 (t, 1H,  $J = 7.4$ ), 6.72 (br s, 1H), 4.99 (s, 1H), 4.47 (br d, 1H,  $J = 8.4$ ), 4.05 - 3.91 (m, 1H), 3.06 (s, 6H), 2.72 - 2.62 (m, 1H), 2.46 - 2.36 (m, 1H), 2.00 - 1.45 (m, 5H), 1.25 (s, 3H), 1.16 (d, 3H,  $J = 7.8$ ), 1.10 (s, 3H); ESI-MS  $m/z$  366 ( $\text{MH}^+$ ).

Example 72:  $N^2, N^4, N^4$ -TRIMETHYL- $N^2, N^6$ -BIS(4-METHYLPHENYL)-2,4,6-PYRIMIDINETRIAMINE: Prepared by Procedures D, E (150°C, 16 hours), and F (5 hours).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.26 (d, 2H,  $J = 8.1$ ), 7.15 (br d, 4H,  $J \sim 8$ ), 7.04 (d, 2H,  $J = 8.1$ ), 6.19 (br s, 1H), 5.29 (s, 1H), 3.50 (s, 3H), 2.94 (s, 6H), 2.36 (s, 3H), 2.29 (s, 3H); ESI-MS  $m/z$  348 ( $\text{MH}^+$ ).

Example 73:  $N^2$ -CYCLOHEXYL- $N^2, N^4, N^4$ -TRIMETHYL- $N^6$ -(4-METHYLPHENYL)-2,4,6-PYRIMIDINETRIAMINE: Prepared by Procedures D, E (150°C, 12 hours), and F (5 hours).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.25 (d, 2H,  $J = 8.4$ ), 7.10 (d, 2H,  $J = 8.1$ ), 6.26 (br s, 1H), 5.22 (s, 1H), 4.66 - 4.52 (m, 1H), 3.01 (s, 3H), 2.99 (s, 6H), 2.32 (s, 3H), 1.87 - 1.64 (m, 5H), 1.52 - 1.35 (m, 4H), 1.22 - 1.06 (m, 1H); ESI-MS  $m/z$  340 ( $\text{MH}^+$ ).

Example 74:  $N^2$ -CYCLOHEXYL- $N^2$ -(2-METHOXYETHYL)- $N^4, N^4$ -DIMETHYL- $N^6$ -(4-METHYLPHENYL)-2,4,6-PYRIMIDINETRIAMINE: Prepared by Procedures H, J (overnight), and F (2 hours).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.28 (d, 2H,  $J = 8.1$ ), 7.11 (d, 2H,  $J = 8.1$ ), 6.19 (br s, 1H), 5.22 (s, 1H), 4.60 - 4.50 (m, 1H), 3.64 - 3.55 (m, 4H), 3.39 (s, 3H), 2.99 (s, 6H), 2.31 (s, 3H), 1.83 - 1.75 (m, 4H), 1.73 - 1.63 (m, 1H), 1.52 - 1.38 (m, 4H), 1.19 - 1.05 (m, 1H); ESI-MS  $m/z$  384

(MH<sup>+</sup>).

Example 75: 2-(2,3-DIHYDRO-1H-INDOL-1-YL)-N<sup>4</sup>,N<sup>4</sup>-DIMETHYL-N<sup>6</sup>-(4-METHYLPHENYL)-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures H, E (150°C, 16 hours), and F (2 hours). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.37 (d, 1H, J = 7.8), 7.26 (d, 2H, J = 7.8), 7.20 - 7.11 (m, 4H), 6.86 (t, 1H, J = 7.8), 6.31 (br s, 1H), 5.39 (s, 1H), 4.24 (t, 4H, J = 8.3), 3.13 (t, 4H, J = 8.3), 3.07 (s, 6H), 2.35 (s, 3H); ESI-MS m/z 346 (MH<sup>+</sup>).

Example 76: N<sup>2</sup>-[2-(1H-3-INDOLYL)ETHYL]-N<sup>4</sup>,N<sup>4</sup>-DIMETHYL-N<sup>6</sup>-(4-METHYLPHENYL)-2,4,6-PYRIMIDINETRIAMINE: Prepared by Procedures H, J, and G. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.19 (br s, 1H), 7.65 (d 1H, J = 7.8), 7.36 (d, 1H, J = 7.8), 7.21 - 7.09 (m, 6H), 7.04 (s, 1H), 6.52 (br s, 1H), 5.28 (s, 1H), 4.95 (br d, 1H, J = 7.2), 3.72 (q, 2H, J = 7.2), 3.06 (t, 2H, J = 7.8), 2.99 (s, 6H), 2.32 (s, 3H); ESI-MS m/z 387 (MH<sup>+</sup>).

Example 77: N<sup>2</sup>-[2-(1H-INDOL-3-YL)ETHYL]-N<sup>2</sup>,N<sup>4</sup>,N<sup>4</sup>-TRIMETHYL-N<sup>6</sup>-(4-METHYLPHENYL)-2,4,6-PYRIMIDINETRIAMINE: Prepared by Procedures H, J, and G or F. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.14 (br s, 1H), 7.70 (d 1H, J = 7.8), 7.32 (d, 1H, J = 7.8), 7.22 (d, 2H, J = 7.8), 7.17 (t, 1H, J = 7.2), 7.12 (t, 1H, J = 7.2), 7.08 (d, 2H, J = 7.8), 6.98 (s, 1H), 6.36 (br s, 1H), 5.25 (s, 1H), 3.90 (t, 2H, J = 7.8), 3.14 (s, 3H), 3.07 (t, 2H, J = 7.8), 2.99 (s, 6H), 2.30 (s, 3H); ESI-MS m/z 401 (MH<sup>+</sup>).

Example 78: N<sup>4</sup>-(3,4-DICHLOROPHENYL)-N<sup>2</sup>-[2-(1H-3-INDOLYL)ETHYL]-N<sup>2</sup>,N<sup>6</sup>,N<sup>6</sup>-TRIMETHYL-2,4,6-

PYRIMIDINETRIAMINE: Prepared by Procedures H, J, and G.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.00 (br s, 1H), 7.75 (s, 1H), 7.68 (d 1H, *J* = 7.8), 7.35 (d, 1H, *J* = 7.8), 7.24 - 7.15 (m, 3H), 7.10 (t, 1H, *J* = 7.2), 7.00 (s, 1H) 6.23 (br s, 1H), 5.15 (s, 1H), 3.90 (t, 2H, *J* = 7.8), 3.14 (s, 3H), 3.08 (t, 2H, *J* = 7.8), 3.03 (s, 6H); ESI-MS *m/z* 455 (MH<sup>+</sup> with <sup>35</sup>Cl), 457 (MH<sup>+</sup> with <sup>37</sup>Cl).

Example 79: N<sup>2</sup>-[2-(1H-INDOL-3-YL)ETHYL]-N<sup>2</sup>,N<sup>4</sup>,N<sup>4</sup>-TRIMETHYL-(2-NAPHTHYL)-6-(1-PIPERIDINYL)-2,4,6-PYRIMIDINETRIAMINE:

Prepared by Procedures D, E (160°C, 28 hours), and G. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.18 (br s, 1H), 7.92 (s, 1H), 7.90 - 7.03 (m, 10H), 6.95 (s, 1H) 6.84 (br s, 1H), 5.34 (s, 1H), 3.90 (t, 2H, *J* = 7.8), 3.17 (s, 3H), 3.07 (t, 2H, *J* = 7.8), 2.96 (s, 6H); ESI-MS *m/z* 437 (MH<sup>+</sup>).

Example 80: 1-[4-(DIMETHYLAMINO)-6-(4-TOLUIDINO)-2-PYRIMIDINYL]-4-PHENYL-4-PIPERIDINOL: Prepared by

Procedures H, E (150°C, 10 hours), and F (3 hours). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.43 (d, 2H, *J* = 7.8), 7.35 (t, 2H, *J* = 7.8), 7.27 - 7.21 (m, 3H), 7.14 (d, 2H, *J* = 7.8), 6.24 (br s, 1H), 6.18 (br s, 1H), 5.28 (s, 1H), 4.43 - 4.37 (m, 2H), 4.03 (t, 2H, *J* = 5.6), 3.06 - 2.97 (m with s at 3.03, 8H), 2.66 - 2.58 (m, 2H), 2.34 (s, 3H).

Example 81: N<sup>4</sup>,N<sup>4</sup>-DIMETHYL-N<sup>6</sup>-(4-METHYLPHENYL)-2-(4-PHENYL-1-PIPERIDINYL)-4,6-PYRIMIDINEDIAMINE: Prepared by

Procedures H, E (150°C, 16 hours), and F (4 hours). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.34 - 7.18 (m, 7H), 7.13 (d, 2H, *J* = 7.8), 6.25 (br s, 1H), 5.28 (s, 1H), 4.94 (d with fine splitting, 2H, *J* = 13.0), 3.01 (s, 6H), 2.87 (dt, 2H, *J* = 1.0, 13.0), 2.74 (tt, 1H, *J* = 11.6, 1.5), 2.32 (s, 3H),



1.90 (d with fine splitting, 2H,  $J = 12.0$ ), 1.72 (ddd, 2H,  $J = 13.0, 12.0, 1.5$ ); ESI-MS  $m/z$  388 ( $MH^+$ ).

5 Example 82:  $N^4, N^4$ -DIMETHYL- $N^6$ -(4-METHYLPHENYL)-2-(3-PHENYL-4-MORPHOLINYL)-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures H, E (150°C, 20 hours), and F (3 hours).  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  7.51 (d, 2H,  $J = 7.8$ ), 7.32 (t, 2H,  $J = 7.8$ ), 7.23 (t, 1H,  $J = 7.8$ ), 7.17 (d, 2H,  $J = 7.8$ ), 7.09 (d, 2H,  $J = 7.8$ ), 6.25 (br s, 1H), 5.88 (d, 1H,  $J = 1.0$ ), 5.27 (s, 1H), 4.49 (t, 2H,  $J = 13.2$ ), 3.94 (m, 2H), 10 3.66 (dt, 1H,  $J = 1.0, 11.5$ ), 3.24 (dt, 1H,  $J = 1.5, 11.5$ ), 2.97 (s, 6H), 2.32 (s, 3H); ESI-MS  $m/z$  390 ( $MH^+$ ).

15 Example 83:  $N^4, N^4$ -DIMETHYL- $N^6$ -(4-METHYLPHENYL)-2-(2-PHENYL-4-MORPHOLINYL)-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures H, E (150°C, 20 hours), and F (3 hours).  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  7.47 (d, 2H,  $J = 7.8$ ), 7.38 (t, 2H,  $J = 7.8$ ), 7.33 (t, 1H,  $J = 7.8$ ), 7.19 (d, 2H,  $J = 7.8$ ), 7.11 (d, 2H,  $J = 7.8$ ), 6.22 (br s, 1H), 5.29 (s, 1H), 20 4.74 (dd, 1H,  $J = 13.2, 1.0$ ), 4.59 - 4.51 (m, 2H), 4.16 - 4.08 (m, 1H), 3.80 (dt, 1H,  $J = 1.0, 11.9$ ), 3.11 (dt, 1H,  $J = 1.5, 12.4$ ), 2.98 (s, 6H), 2.90 (dd, 1H,  $J = 10.6, 11.9$ ), 2.33 (s, 3H); ESI-MS  $m/z$  390 ( $MH^+$ ).

25 Example 84:  $N^4, N^4$ -DIMETHYL- $N^6$ -(4-METHYLPHENYL)-2-{4-[(4-METHYLPHENYL) SULFONYL]-1-PIPERAZINYL}-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures H, E (150°C, overnight), and F (3 hours).  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  7.65 (d, 2H,  $J = 8.3$ ), 7.31 (d, 2H,  $J = 8.3$ ), 7.15 (d, 30 2H,  $J = 8.4$ ), 7.11 (d, 2H,  $J = 7.2$ ), 6.20 (br s, 1H), 5.22 (s, 1H), 3.87 (t, 4H,  $J = 4.2$ ), 3.02 (t, 4H,  $J = 4.2$ ), 2.95 (s, 6H), 2.43 (s, 3H), 2.33 (s, 3H); ESI-MS

$m/z$  467 ( $MH^+$ ).

Example 85:  $N^4, N^4$ -DIMETHYL- $N^6$ -(4-METHYLPHENYL)-2-[4-(2-METHYLPHENYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE:

5 Prepared by Procedures D, E (160°C, 12 hours), and F (12 hours).  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  7.23 - 7.10 (m, 6H), 7.02 - 6.96 (m, 2H), 6.28 (br s, 1H), 5.28 (s, 1H), 3.95 - 3.86 (m, 4H), 2.99 (s, 6H), 2.96 - 2.92 (m, 4H), 2.36 (s, 3H), 2.32 (s, 3H); ESI-MS  $m/z$  403 ( $MH^+$ ).

10

Example 86:  $N^4, N^4$ -DIMETHYL- $N^6$ -(4-METHYLPHENYL)-2-[4-(3-METHYLPHENYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedures D, E (160°C, 12 hours), and F (12 hours).  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  7.19 (d, 2H,  $J$  = 7.8), 7.17 (t, 1H,  $J$  = 7.8), 7.11 (d, 2H,  $J$  = 7.8), 6.91 (s, 1H), 6.89 (d, 1H,  $J$  = 7.8), 6.69 (d, 1H,  $J$  = 7.8), 6.33 (br s, 1H), 5.29 (s, 1H), 3.93 (t, 4H,  $J$  = 5.1), 3.22 (t, 4H,  $J$  = 5.1), 3.01 (s, 6H), 2.33 (s, 6H); ESI-MS  $m/z$  403 ( $MH^+$ ).

20

Example 87:  $N^4, N^4$ -DIMETHYL- $N^6$ -(4-METHYLPHENYL)-2-[4-(4-METHYLPHENYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedures D, E (160°C, 36 hours), and F (8 hours).  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  7.19 (d, 2H,  $J$  = 9.0), 7.16 (d, 2H,  $J$  = 8.7), 7.10 (d, 2H,  $J$  = 9.0), 6.90 (d, 2H,  $J$  = 8.4), 6.24 (br s, 1H), 5.27 (s, 1H), 3.93 (t, 4H,  $J$  = 4.8), 3.18 (t, 4H,  $J$  = 5.1), 3.00 (s, 6H), 2.33 (s, 3H), 2.28 (s, 3H); ESI-MS  $m/z$  403 ( $MH^+$ ).

30

Example 88:  $N^4, N^4$ -DIMETHYL- $N^6$ -(4-METHYLPHENYL)-2-[4-[3-(TRIFLUOROMETHYL)-2-PYRIDINYL]-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures H, E (16

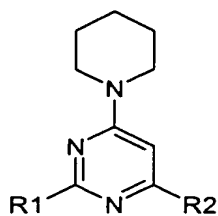
hours), and F.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.57 (dd, 1H,  $J$  = 4.4, 2.2), 7.87 (dd, 1H,  $J$  = 7.8, 2.2), 7.20 (d, 2H,  $J$  = 8.1), 7.13 (d, 2H,  $J$  = 8.1), 6.98 (dd, 1H,  $J$  = 7.8, 4.4), 6.24 (br s, 1H), 5.28 (s, 1H), 3.90 (t, 4H,  $J$  = 4.8), 3.36 (t, 4H,  $J$  = 4.8), 3.00 (s, 6H), 2.32 (s, 3H); ESI-MS  $m/z$  458 ( $\text{MH}^+$ ).

Example 89: N-(4-METHYLPHENYL)-2-(1-PIPERIDINYL)-6-{4-[3-(TRIFLUOROMETHYL)-2-PYRIDINYL]-1-PIPERAZINYL}-4-

10 PYRIMIDINAMINE: Prepared by Procedures M, E (120°C, for addition of piperidine), and F.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.43 (dd, 1H,  $J$  = 4.4, 2.2), 7.87 (dd, 1H,  $J$  = 7.8, 2.2), 7.19 (d, 2H,  $J$  = 8.1), 7.12 (d, 2H,  $J$  = 8.1), 6.99 (dd, 1H,  $J$  = 7.8, 4.4), 6.28 (br s, 1H), 5.35 (s, 1H),  
15 3.77 - 3.72 (m, 4H), 3.62 (t, 4H,  $J$  = 4.8), 3.33 (t, 4H,  $J$  = 4.8), 2.33 (s, 3H), 1.69 - 1.52 (m, 6H); ESI-MS  $m/z$  498 ( $\text{MH}^+$ ).

Example 90: 6-[2-(METHOXYMETHYL)-1-PIPERIDINYL]-N-(4-METHYLPHENYL)-2-{4-[3-(TRIFLUOROMETHYL)-2-PYRIDINYL]-1-

20 PIPERAZINYL}-4-PYRIMIDINAMINE: Prepared by Procedures D, J (90°C, overnight), and F (2 hours).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.44 (dd, 1H,  $J$  = 4.4, 2.2), 7.88 (dd, 1H,  $J$  = 7.8, 2.2), 7.20 (d, 2H,  $J$  = 8.1), 7.12 (d, 2H,  $J$  = 8.1),  
25 6.99 (dd, 1H,  $J$  = 7.8, 4.4), 6.23 (br s, 1H), 5.38 (s, 1H), 4.68 - 4.54 (m, 1H), 4.15 - 4.03 (m, 1H), 3.90 (t, 4H,  $J$  = 4.8), 3.57 (t, 1H,  $J$  = 9.7), 3.44 - 3.35 (m, 5H), 3.34 (s, 3H), 2.81 (t, 1H,  $J$  = 12.0), 2.33 (s, 3H), 1.93 - 1.86 (m, 1H), 1.72 - 1.41 (m, 3H), 1.29 - 1.25 (m, 1H),  
30 0.91 - 0.86 (m, 1H); ESI-MS  $m/z$  542 ( $\text{MH}^+$ ).

Table 1  
continued

Example	substitution		Ki (nM)		
	R1	R2	GalR1	GalR2	GalR3
37			>5000	903	343
38			2901	516	320
39			>5000	>5000	128
40			>5000	2623	164
41			2131	840	151
42			>5000	1137	275
43			>5000	>5000	107
44			>5000	1023	133
45			>5000	>5000	505

Example 115: N-4-[3-(BENZYLOXY)PHENYL]-N-6-,N-6-DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedures A (CH<sub>2</sub>Cl<sub>2</sub>, Et<sub>3</sub>N, Me<sub>2</sub>NHCl, stirred 3.5 h at -78 °C, warmed to 0 °C and stirred 3 h), N, and

5 O. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.23 - 8.19 (m, 1H), 7.52 (dt, 1H, J = 1.9, 7.2), 7.43 - 7.20 (m, 7H), 6.96 (s, 1H), 6.88 (d, 1H, J = 8.0), 6.80 (d, 1H, J = 8.1), 6.69 - 6.63 (m, 2H), 5.34 (s, 1H), 5.03 (s, 2H), 4.03 - 3.97 (m, 4H), 3.66 (t, 4H, J = 5.2), 3.02 (s, 6H); ESI-MS m/z 482 (MH<sup>+</sup>).

10

Example 116: 4-{4-[4-(DIMETHYLAMINO)-6-(4-TOLUIDINO)-2-PYRIMIDINYL]-1-PIPERAZINYL}PHENOL: Prepared by Procedures

A (CH<sub>2</sub>Cl<sub>2</sub>, Et<sub>3</sub>N, Me<sub>2</sub>NHCl, stirred 3.5 h at -78 °C, warmed to 0 °C and stirred 3 h), N, and O. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 10.04 (s, 1H), 7.19 - 7.14 (m, 4H), 6.85 - 6.79 (m, 4H), 5.31 (s, 1H), 5.22 (s, 1H), 3.96 (t, 4H, J = 5.1), 3.05 (t, 4H, J = 5.0), 3.03 (s, 6H), 2.34 (s, 3H); FIAMS m/z 405 (MH<sup>+</sup>).

15

20

Example 117: N<sup>4</sup>-[4-(BENZYLOXY)PHENYL]-N<sup>6</sup>,N<sup>6</sup>-DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedures A (CH<sub>2</sub>Cl<sub>2</sub>, Et<sub>3</sub>N, Me<sub>2</sub>NHCl, stirred 3.5 h at -78 °C, warmed to 0 °C and stirred 3 h), N, and

O.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.21 (dd, 1H,  $J = 1.9, 5.6$ ),  
 7.55 - 7.27 (m, 7H), 7.24 - 7.16 (m, 2H), 7.04 - 6.91 (m,  
 2H), 6.69 - 6.64 (m, 2H), 5.06 (s, 2H), 5.05 (s, 1H),  
 4.08 - 3.97 (m, 4H), 3.69 (t, 4H,  $J = 5.1$ ), 3.03 (s, 6H);  
 5 ESI-MS  $m/z$  482 ( $\text{MH}^+$ ).

Example 118:  $N^4$ -(1,3-BENZODIOXOL-5-YL)- $N^6$ , $N^6$ -DIMETHYL-2-  
[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedures A ( $\text{CH}_2\text{Cl}_2$ ,  $\text{Et}_3\text{N}$ ,  $\text{Me}_2\text{NHHCl}$ , stirred  
 10 3.5 h at  $-78^\circ\text{C}$ , warmed to  $0^\circ\text{C}$  and stirred 3 h), N, and  
 O.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.24 - 8.18 (m, 1H), 7.48  
 (dt, 1H,  $J = 1.9, 8.1$ ), 6.92 (d, 1H,  $J = 1.9$ ), 6.75 (d,  
 1H,  $J = 8.2$ ), 6.74 - 6.54 (m, 3H), 6.41 (br s, 1H), 5.95  
 (s, 2H), 5.16 (s, 1H), 3.89 (t, 4H,  $J = 5.1$ ), 3.60 (t,  
 15 4H,  $J = 5.3$ ), 2.99 (s, 6H); ESI-MS  $m/z$  420 ( $\text{MH}^+$ ).

Example 119:  $N^4$ -(2,3-DIHYDRO-1,4-BENZODIOXIN-6-YL)- $N^6$ , $N^6$ -  
DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-

PYRIMIDINEDIAMINE: Prepared by Procedures A ( $\text{CH}_2\text{Cl}_2$ ,  $\text{Et}_3\text{N}$ ,  
 20  $\text{Me}_2\text{NHHCl}$ , stirred 3.5 h at  $-78^\circ\text{C}$ , warmed to  $0^\circ\text{C}$  and  
 stirred 3 h), N, and O.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.24 -  
 8.18 (m, 1H), 7.49 (dt, 1H,  $J = 2.1, 7.1$ ), 6.89 (d, 1H,  $J$   
 = 2.2), 6.81 (d, 1H,  $J = 8.6$ ), 6.76 (d, 1H,  $J = 2.4$ ),  
 6.68 (d, 1H,  $J = 8.5$ ), 6.62 (dd, 1H,  $J = 4.6, 7.0$ ), 6.18

(br s, 1H), 5.21 (s, 1H), 4.33 - 4.15 (m, 4H), 3.89 (t, 4H,  $J = 5.1$ ), 3.61 (t, 4H,  $J = 5.1$ ), 3.00 (s, 6H); ESI-MS  $m/z$  434 ( $MH^+$ ).

5 Example 120:  $N^4$ -(4-ISOQUINOLINYL)- $N^6,N^6$ -DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures A ( $CH_2Cl_2$ ,  $Et_3N$ ,  $Me_2NH\cdot HCl$ , stirred 3.5 h at -78 °C, warmed to 0 °C and stirred 3 h), N, and O.  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  8.93 (d, 1H,  $J = 1.5$ ), 8.31 (d, 1H,  $J =$   
10 2.6), 8.27 - 8.19 (m, 1H), 8.01 (d, 1H,  $J = 8.2$ ), 7.70 (d, 1H,  $J = 7.8$ ), 7.59 - 7.52 (m, 1H), 7.51 - 7.45 (m, 2H), 6.78 (br s, 1H), 6.68 (d, 1H,  $J = 8.6$ ), 6.63 (dd, 1H,  $J = 5.0, 7.1$ ), 5.29 (s, 1H), 3.94 (t, 4H,  $J = 5.0$ ), 3.63 (t, 4H,  $J = 5.3$ ), 3.01 (s, 6H); ESI-MS  $m/z$  427 ( $MH^+$ ).

15

Example 121:  $N^4$ -(4-CYCLOHEXYLPHENYL)- $N^6,N^6$ -DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedures A ( $CH_2Cl_2$ ,  $Et_3N$ ,  $Me_2NH\cdot HCl$ , stirred 3.5 h at -78 °C, warmed to 0 °C and stirred 3 h), N, and  
20 O.  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  8.25 - 8.19 (m, 1H), 7.49 (dt, 1H,  $J = 2.0, 6.9$ ), 7.22 (d, 2H,  $J = 6.4$ ), 7.16 (d, 2H,  $J = 8.2$ ), 6.68 (d, 1H,  $J = 8.6$ ), 6.66 - 6.60 (m, 1H), 6.21 (br s, 1H), 5.30 (s, 1H), 3.99 - 3.91 (m, 4H), 3.63 (t, 4H,  $J = 5.2$ ), 3.02 (s, 6H), 2.53 - 2.42 (m, 1H), 1.92

- 1.79 (m, 4H), 1.48 - 1.32 (m, 4H), 1.31 - 1.19 (m, 2H);  
ESI-MS  $m/z$  458 ( $MH^+$ ).

Example 122:  $N^4, N^4$ -DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]- $N^6$ -(5,6,7,8-TETRAHYDRO-1-NAPHTHALENYL)-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures A ( $CH_2Cl_2$ ,  $Et_3N$ ,  $Me_2NH\cdot HCl$ , stirred 3.5 h at  $-78^\circ C$ , warmed to  $0^\circ C$  and stirred 3 h), N, and O.  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  8.20 (dd, 1H,  $J = 1.3, 4.9$ ), 7.50 (dt, 1H,  $J = 2.2, 6.8$ ), 7.17 (d, 1H,  $J = 7.5$ ), 7.09 (t, 1H,  $J = 7.6$ ), 6.94 (d, 1H,  $J = 7.7$ ), 6.73 - 6.62 (m, 2H), 5.06 (s, 1H), 4.08 - 3.93 (m, 4H), 3.66 (t, 4H,  $J = 5.3$ ), 3.00 (s, 6H), 2.79 (t, 2H,  $J = 6.0$ ), 2.72 (t, 2H,  $J = 5.9$ ), 1.88 - 1.67 (m, 4H), NH (1H, unobserved); ESI-MS  $m/z$  430 ( $MH^+$ ).

15

Example 123:  $N^4$ -(2,3-DIHYDRO-1H-INDEN-5-YL)- $N^6, N^6$ -DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures A ( $CH_2Cl_2$ ,  $Et_3N$ ,  $Me_2NH\cdot HCl$ , stirred 3.5 h at  $-78^\circ C$ , warmed to  $0^\circ C$  and stirred 3 h), N, and O.  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  8.20 (d, 1H,  $J = 4.8$ ), 7.51 (dt, 1H,  $J = 1.8, 6.9$ ), 7.19 (d, 1H,  $J = 7.6$ ), 7.14 (s, 1H), 7.04 (dd, 1H,  $J = 1.7, 7.7$ ), 6.73 -

20



6.61 (m, 2H), 5.23 (s, 1H), 4.09 - 3.94 (m, 4H), 3.68 (t, 4H,  $J = 5.9$ ), 3.04 (s, 6H), 2.89 (t, 4H,  $J = 7.8$ ), 2.16 - 2.01 (m, 2H), NH (1H, unobserved); ESI-MS  $m/z$  416 ( $MH^+$ ).

5     Example 124:  $N^4$ -(3,4-DICHLOROPHENYL)- $N^6$ , $N^6$ -DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedures A ( $CH_2Cl_2$ ,  $Et_3N$ ,  $Me_2NHCl$ , stirred 3.5 h at  $-78^\circ C$ , warmed to  $0^\circ C$  and stirred 3 h), N, and O.  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  8.31 - 8.20 (m, 1H), 7.79 - 7.69 (m, 1H), 7.61 - 7.44 (m, 1H), 7.42 - 7.28 (m, 1H), 7.25 - 7.11 (m, 1H), 6.79 - 6.61 (m, 2H), 6.42 (br s, 1H), 5.22 (s, 1H), 3.98 - 3.82 (m, 4H), 3.65 - 3.56 (m, 4H), 3.02 (s, 6H); ESI-MS  $m/z$  444 ( $MH^+$  with  $^{35}Cl$ ,  $^{35}Cl$ ), 446 ( $MH^+$  with  $^{35}Cl$ ,  $^{37}Cl$ ), 448 ( $MH^+$  with  $^{37}Cl$ ,  $^{37}Cl$ ).

15

Example 125:  $N^4$ , $N^4$ -DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]- $N^6$ -[3-(TRIFLUOROMETHYL)PHENYL]-4,6-

PYRIMIDINEDIAMINE: Prepared by Procedures A ( $CH_2Cl_2$ ,  $Et_3N$ ,  $Me_2NHCl$ , stirred 3.5 h at  $-78^\circ C$ , warmed to  $0^\circ C$  and stirred 3 h), N, and O.  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  8.59 (br s, 1H), 8.24 - 8.18 (m, 1H), 7.86 (s, 1H), 7.78 - 7.22 (m, 4H), 6.65 (t, 2H,  $J = 5.0$ ), 5.29 (s, 1H), 3.96 (t, 4H,  $J = 5.5$ ), 3.64 (t, 4H,  $J = 5.2$ ), 3.03 (s, 6H); ESI-MS  $m/z$  444 ( $MH^+$ ).

20

Example 126: 2-(4-BENZYL-1-PIPERAZINYL)-N<sup>4</sup>-[3-(DIMETHYLAMINO)PHENYL]-N<sup>6</sup>,N<sup>6</sup>-DIMETHYL-4,6-

PYRIMIDINEDIAMINE: Prepared by Procedures P (toluene, 95 °C, 16 h), Q (dioxane, 120 °C), and A. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.52 - 7.37 (m, 7H), 7.25 (t, 1H, J = 2.0), 7.14 (dd, 1H, J = 1.5, 8.2), 7.05 (dd, 1H, J = 2.5, 8.2), 4.36 (s, 2H), 3.98 (br s, 4H), 3.36 (s, 4H), 3.11 (s, 6H), 3.05 (s, 6H), 2.60 (s, 1H); ESI-MS m/z 432 (MH<sup>+</sup>).

Example 127: 2-(4-BENZYL-1-PIPERAZINYL)-N<sup>4</sup>,N<sup>4</sup>-DIMETHYL-N<sup>6</sup>-(2-METHYL-1,3-BENZOTHAZOL-5-YL)-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedures P (130 °C, 13 h), Q, and A. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.12 (s, 1H), 7.87 (d, 1H, J = 8.8), 7.52 - 7.38 (m, 6H), 5.58 (s, 1H), 4.58 (s, 1H), 4.30 (s, 2H), 3.79 - 3.42 (m, 4H), 3.22 - 2.91 (m, 4H), 3.09 (s, 6H), 2.98 (s, 3H); ESI-MS m/z 460 (MH<sup>+</sup>).

Example 128: 2-(4-BENZYL-1-PIPERAZINYL)-N<sup>4</sup>-CYCLOHEPTYL-

N<sup>6</sup>,N<sup>6</sup>-DIMETHYL-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures P (140 °C, toluene, 6 h), Q, and A. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.20 - 7.09 (m, 5H), 4.78 (s, 1H), 4.18 (br s, 1H), 3.74 (t, 4H, J = 5.2), 3.52 (s, 2H), 2.99 (s,

6H), 2.46 (t, 4H,  $J = 5.1$ ), 2.03 - 1.92 (m, 2H), 1.87 - 1.68 (m, 11H); ESI-MS  $m/z$  409 ( $MH^+$ ).

Example 129: 4-{[2-(4-BENZYL-1-PIPERAZINYL)-6-(DIMETHYLAMINO)-4-PYRIMIDINYL]AMINO}-2-

5

CHLOROBENZONITRILE: Prepared by Procedures P (toluene, 95 °C, 16 h), Q (dioxane, 120 °C), and A.  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.88 (d, 1H,  $J = 3.1$ ), 7.48 (d, 1H,  $J = 8.5$ ), 7.42 - 7.22 (m, 6H), 6.45 (s, 1H), 5.20 (s, 1H), 3.79 (t, 4H,  $J = 5.2$ ), 3.55 (s, 2H), 3.02 (s, 6H), 2.51 (t, 4H,  $J = 5.0$ ); ESI-MS  $m/z$  448 ( $MH^+$  with  $^{35}Cl$ ), 450 ( $MH^+$  with  $^{37}Cl$ ).

10

Example 130: 2-(4-BENZYL-1-PIPERAZINYL)- $N^4,N^4$ -DIMETHYL- $N^6$ -(1,3,3-TRIMETHYLBICYCLO[2.2.1]HEPT-2-YL)-4,6-

15

PYRIMIDINEDIAMINE: Prepared by procedures P (toluene, 95 °C, 16 h), Q (dioxane, 120 °C), and A.  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.38 - 7.21 (m, 6H), 4.87 (s, 1H), 3.79 - 3.69 (m, 4H), 3.53 (s, 2H), 3.46 (s, 1H), 2.98 (s, 6H), 2.46 (t, 4H,  $J = 5.1$ ), 1.71 (s, 1H), 1.69 - 1.62 (m, 2H), 1.48 - 1.35 (m, 2H), 1.20 (d, 1H,  $J = 10.2$ ), 1.19 - 1.02 (m, 1H), 1.14 (s, 3H), 1.07 (s, 3H), 0.79 (s, 3H); ESI-MS  $m/z$  449 ( $MH^+$ ).

20

Example 131: 2-{4-[3-(BENZYLOXY) PHENYL]-1-PIPERAZINYL}-  
N<sup>4</sup>,N<sup>4</sup>-DIMETHYL-N<sup>6</sup>-(4-METHYLPHENYL)-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedures A (CH<sub>2</sub>Cl<sub>2</sub>, TEA, 3 - 4 h at -78 °C,  
then 3 - 4 h at 0 °C), N, and O. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ  
5 7.44 (d, 2H, J = 7.1), 7.36 (t, 2H, J = 7.0), 7.29 (d,  
1H, J = 7.1), 7.22 - 7.04 (m, 5H), 6.58 - 6.52 (m, 2H),  
6.48 (d, 1H, J = 7.2), 5.29 (s, 1H), 5.21 (s, 1H), 5.03  
(s, 2H), 3.89 - 3.80 (m, 4H), 3.28 - 3.15 (m, 4H), 3.00  
(s, 6H), 2.30 (s, 3H); ESI-MS m/z 495 (MH<sup>+</sup>).

10

Example 132: N<sup>4</sup>,N<sup>4</sup>-DIMETHYL-2-[4-(2-PYRIDINYL)-1-  
PIPERAZINYL]-N<sup>6</sup>-(3-QUINOLINYL)-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedures A (CH<sub>2</sub>Cl<sub>2</sub>, TEA, 3 - 4 h at -78 °C,  
then 3 - 4 h at 0 °C), N, and O. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ  
15 8.93 (d, 1H, J = 2.6), 8.31 (d, 1H, J = 2.5), 8.26 - 8.18  
(m, 1H), 8.02 (d, 1H, J = 8.2), 7.71 (d, 1H, J = 7.7),  
7.57 (dt, 1H, J = 1.5, 5.3), 7.53 - 7.46 (m, 2H), 6.68  
(d, 1H, J = 8.6), 6.64 (dd, 1H, J = 4.9, 7.1), 5.30 (d,  
2H, J = 3.7), 3.94 (t, 4H, J = 4.9), 3.64 (t, 4H, J =  
20 5.4), 3.03 (s, 6H);  
ESI-MS m/z 427 (MH<sup>+</sup>).

Example 133: N<sup>4</sup>-[4-BROMO-3-(TRIFLUOROMETHYL) PHENYL]-N<sup>6</sup>,N<sup>6</sup>-  
DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-

PYRIMIDINEDIAMINE: Prepared by Procedures A (CH<sub>2</sub>Cl<sub>2</sub>, TEA, 3 - 4 h at -78 °C, then 3 - 4 h at 0 °C), N, and O. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.23 - 8.19 (m, 1H), 8.17 (d, 1H, *J* = 2.3), 7.57 (d, 1H, *J* = 8.7), 7.53 - 7.47 (m, 1H), 7.39 (d, 1H, *J* = 5.2), 6.69 (d, 1H, *J* = 8.7), 6.64 (t, 1H, *J* = 5.0), 6.27 (s, 1H), 5.19 (s, 1H), 3.94 - 3.87 (m, 4H), 3.65 - 3.59 (m, 4H), 3.04 (s, 6H); ESI-MS *m/z* 522 (MH<sup>+</sup> with <sup>79</sup>Br), 524 (MH<sup>+</sup> with <sup>81</sup>Br).

10 Example 134: N<sup>4</sup>-{3-CHLORO-4-[(TRIFLUOROMETHYL)SULFANYL]PHENYL}-N<sup>6</sup>,N<sup>6</sup>-DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures A (CH<sub>2</sub>Cl<sub>2</sub>, TEA, 3 - 4 h at -78 °C, then 3 - 4 h at 0 °C), N, and O. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.23 - 8.19 (m, 1H), 7.91 (d, 1H, *J* = 2.3), 7.61 (d, 1H, *J* = 8.5), 7.50 (dt, 1H, *J* = 2.1, 8.5), 7.30 - 7.20 (m, 1H), 6.70 (d, 1H, *J* = 9.1), 6.64 (dd, 1H, *J* = 4.7, 7.1), 6.35 (br s, 1H), 5.26 (s, 1H), 3.92 (t, 4H, *J* = 5.6), 3.64 (t, 4H, *J* = 5.0), 3.06 (s, 6H); ESI-MS *m/z* 510 (MH<sup>+</sup> with <sup>35</sup>Cl), 512 (MH<sup>+</sup> with <sup>37</sup>Cl).

Example 135: N<sup>4</sup>-(3-ETHOXYPHENYL)-N<sup>6</sup>,N<sup>6</sup>-DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures A (CH<sub>2</sub>Cl<sub>2</sub>, TEA, 3 - 4 h at -78 °C, then 3 -

4 h at 0 °C), N, and O. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.28 - 8.19 (m, 1H), 7.50 (dt, 1H, *J* = 2.1, 6.9), 7.19 (t, 1H, *J* = 8.1), 6.96 (t, 1H, *J* = 2.1), 6.85 (d, 1H, *J* = 8.2), 6.68 (d, 1H, *J* = 8.6), 6.63 - 6.56 (m, 1H), 6.35 (br s, 1H), 5.36 (s, 1H), 4.09 - 3.98 (m, 2H), 3.91 (t, 4H, *J* = 5.3), 3.61 (t, 4H, *J* = 5.1), 3.02 (s, 6H), 1.39 (t, 3H, *J* = 5.7); ESI-MS *m/z* 420 (MH<sup>+</sup>).

Example 136: N<sup>4</sup>-[2-CHLORO-4-(TRIFLUOROMETHYL)PHENYL]-N<sup>6</sup>,N<sup>6</sup>-DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures A (CH<sub>2</sub>Cl<sub>2</sub>, TEA, 3 - 4 h at -78 °C, then 3 - 4 h at 0 °C), N, and O. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.23 - 8.15 (m, 1H), 8.15 (d, 1H, *J* = 2.1), 7.50 (dt, 1H, *J* = 2.0, 8.8), 7.42 - 7.33 (m, 2H), 6.69 (d, 1H, *J* = 8.6), 6.64 (dd, 1H, *J* = 4.8, 6.3), 6.28 (s, 1H), 5.18 (s, 1H), 3.91 (t, 4H, *J* = 5.0), 3.62 (t, 4H, *J* = 5.1), 3.04 (s, 6H); ESI-MS *m/z* 478 (MH<sup>+</sup> with <sup>35</sup>Cl), 480 (MH<sup>+</sup> with <sup>37</sup>Cl).

Example 137: N-4-(2-ADAMANTYL)-2-(4-BENZYL-1-PIPERAZINYL)-N-6-N-6-DIMETHYL-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures P (toluene, 90 °C), Q, and A. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.39 - 7.21 (m, 5H), 4.83 (s, 1H), 4.72 (br s, 1H), 3.74 (m, 3H), 3.52 (s, 2H), 2.98 (s,

6H), 2.46 (t, 4H,  $J = 5.3$ ), 2.05 - 1.53 (m, 13H); ESI-MS  $m/z$ : 433 ( $MH^+$ ).

Example 138: N-4-(1-NORADAMANTYL)-2-(4-BENZYL-1-PIPERAZINYL)-N-6-N-6-DIMETHYL-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedures P (toluene, 90 °C), Q, and A.  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.38 - 7.20 (m, 5H), 4.97 (s, 1H), 4.67 (br s, 1H), 3.74 (s, 4H), 3.52 (s, 2H), 2.99 (s, 6H), 2.46 (t, 4H,  $J = 5.2$ ), 2.32 - 1.51 (m, 15H); ESI-MS  $m/z$ : 447 ( $MH^+$ ).

Example 139: 2-(4-BENZYL-1-PIPERAZINYL)-N<sup>4</sup>,N<sup>4</sup>-DIMETHYL-N<sup>6</sup>-[(1S,2R,3R,5S)-2,6,6-TRIMETHYLBICYCLO[3.1.1]HEPT-3-YL]-

4,6-PYRIMIDINEDIAMINE: Prepared by Procedures P (toluene, 150 °C, 4 h), Q (neat, 130 °C), and A.  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.38 - 7.21 (m, 5H), 4.86 (s, 1H), 4.35 (br s, 1H), 3.75 (t, 4H,  $J = 4.6$ ), 3.53 (s, 2H), 2.99 (s, 6H), 2.66 - 2.56 (m, 1H), 2.47 (t, 4H,  $J = 4.5$ ), 2.41 - 2.33 (m, 1H), 1.98 - 1.92 (m, 1H), 1.83 (t, 1H,  $J = 5.8$ ), 1.68 - 1.60 (m, 2H), 1.23 (s, 3H), 1.14 (d, 3H,  $J = 7.3$ ), 1.05 (s, 3H), 0.92 (d, 2H); ESI-MS  $m/z$ : 449 ( $MH^+$ ).

Example 140: 2-[4-(5-BROMO-2-PYRIDINYL)-1-PIPERAZINYL]-  
N<sup>4</sup>,N<sup>4</sup>-DIMETHYL-N<sup>6</sup>-(4-METHYLPHENYL)-4,6-PYRIMIDINEDIAMINE:

Prepared using Procedure Y (DMF). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  
 δ 8.21 (d, 1H, J = 2.6), 7.53 (dd, 1H, J = 2.6, 8.8),  
 5 7.19 (d, 2H, J = 8.5), 7.12 (d, 2H, J = 8.5), 6.21 (s,  
 1H), 5.28 (s, 1H), 3.88 (t, 4H, J = 5.0), 3.58 (t, 4H, J  
 = 5.2), 3.00 (s, 6H), 2.33 (s, 3H); ESI-MS m/z: 468 (MH<sup>+</sup>  
 with <sup>79</sup>Br), 470 (MH<sup>+</sup> with <sup>81</sup>Br).

10 Example 141: 6-{4-[4-(DIMETHYLAMINO)-6-(4-TOLUDINO)-2-  
PYRIMIDINYL]-1-PIPERAZINYL}NICOTINAMIDE: Prepared by

Procedure Y (DMF). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.13 (s, 1H),  
 7.30 - 7.25 (m, 4H), 7.17 (d, 2H, J = 8.5), 7.13 (d, 2H,  
 J = 8.6), 6.18 (br s, 1H), 5.28 (s, 1H), 3.82 (t, 2H, J =  
 15 5.1), 3.79 (t, 2H, J = 5.3), 3.60 (t, 2H, J = 5.1), 3.41  
 (t, 2H, J = 5.3), 2.99 (s, 6H), 2.33 (s, 3H); ESI-MS m/z:  
 433 (MH<sup>+</sup>).

Example 142: 2-[4-(3-METHOXYBENZYL)-1-PIPERAZINYL]-N<sup>4</sup>,N<sup>4</sup>-  
20 DIMETHYL-N<sup>6</sup>-(4-METHYLPHENYL)-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedure Z (DIEA). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ  
 7.22 (d, 1H, J = 6.8), 7.17 (d, 2H, J = 8.3), 7.10 (d,



2H,  $J = 8.2$ ), 6.93 (d, 1H,  $J = 2.3$ ), 6.92 (d, 1H,  $J = 2.4$ ), 6.80 (dd, 1H,  $J = 2.0, 7.6$ ), 6.18 (br s, 1H), 5.25 (s, 1H), 3.82 (s, 3H), 3.78 (t, 4H,  $J = 5.1$ ), 3.52 (s, 2H), 2.97 (s, 6H), 2.49 (t, 4H,  $J = 5.1$ ), 2.31 (s, 3H);

5 ESI-MS  $m/z$ : 433 ( $MH^+$ ).

Example 143: 2-[4-(5-BROMO-2-PYRIDINYL)-1-PIPERAZINYL]- $N^4$ -(3-METHOXYPHENYL)- $N^6, N^6$ -DIMETHYL-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedure Y.  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  8.21  
 10 (d, 1H,  $J = 2.4$ ), 7.53 (dd, 1H,  $J = 2.5, 9.2$ ), 7.20 (t, 1H,  $J = 8.1$ ), 7.00 (t, 1H,  $J = 2.0$ ), 6.85 (dd, 1H,  $J = 2.0, 8.0$ ), 6.62 - 6.54 (m, 2H), 6.29 (s, 1H), 5.36 (s, 1H), 3.89 (t, 4H,  $J = 5.1$ ), 3.80 (s, 3H), 3.58 (t, 4H,  $J = 4.9$ ), 3.02 (s, 6H); ESI-MS  $m/z$ : 484 ( $MH^+$  with  $^{79}Br$ ), 486  
 15 ( $MH^+$  with  $^{81}Br$ ).

Example 144:  $N^4$ -(3-METHOXYPHENYL)- $N^6, N^6$ -DIMETHYL-2-[4-(2-PYRIDINYLMETHYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedure X.  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  8.61 -  
 20 8.54 (m, 1H), 7.66 (dt, 1H,  $J = 1.8, 7.8$ ), 7.45 (d, 1H,  $J = 7.8$ ), 7.23 - 7.14 (m, 2H), 7.00 (t, 1H,  $J = 2.5$ ), 6.87 - 6.78 (m, 1H), 6.61 - 6.54 (m, 1H), 6.26 (br s, 1H),

5.33 (s, 1H), 3.82 (t, 4H,  $J = 5.0$ ), 3.78 (s, 3H), 3.70 (s, 2H), 2.99 (s, 6H), 2.56 (t, 4H,  $J = 5.0$ ); ESI-MS  $m/z$ : 420 ( $MH^+$ ).

5     Example 145: 2-[4-(CYCLOHEXYLMETHYL)-1-PIPERAZINYL]- $N^4$ -(3-METHOXYPHENYL)- $N^6$ , $N^6$ -DIMETHYL-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedure T.  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.21 (t, 1H,  $J = 8.2$ ), 7.00 - 6.95 (m, 1H), 6.85 (d, 1H,  $J = 8.2$ ), 6.59 (d, 1H,  $J = 7.7$ ), 6.32 (s, 1H), 5.36 (s, 1H),  
 10     3.82 - 3.71 (m, 4H), 3.79 (s, 3H), 3.69 - 3.62 (m, 2H), 3.58 - 3.50 (m, 2H), 3.01 (s, 6H), 2.54 - 2.45 (m, 1H), 1.87 - 1.48 (m, 8H), 1.45 - 1.29 (m, 4H); ESI-MS  $m/z$ : 425 ( $MH^+$ ).

15     Example 146:  $N^4$ -(3-METHOXYPHENYL)- $N^6$ , $N^6$ -DIMETHYL-2-[4-(3-THIENYLMETHYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedures T (reduction 4 h) and W.  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.27 (dd, 1H,  $J = 3.2, 5.1$ ), 7.19 (t, 1H,  $J = 8.0$ ), 7.16 - 7.11 (m, 1H), 7.08 (dd, 1H,  $J = 1.3, 4.9$ ),  
 20     7.00 (t, 1H,  $J = 2.3$ ), 6.82 (dd, 1H,  $J = 2.0, 8.3$ ), 6.57 (dd, 1H,  $J = 2.5, 8.2$ ), 6.25 (s, 1H), 5.33 (s, 1H),

3.79 (t, 4H,  $J = 5.5$ ), 3.78 (s, 3H), 3.57 (s, 2H), 2.99 (s, 6H), 2.48 (t, 4H,  $J = 5.2$ )

ESI-MS  $m/z$ : 425 ( $MH^+$ ).

5 Example 147:  $N^4$ -(3-METHOXYPHENYL)- $N^6,N^6$ -DIMETHYL-2-[4-(4-PYRIDINYLMETHYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedure T (acylation with DIPEA).  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  8.55 (dd, 2H,  $J = 1.5, 5.8$ ), 7.31 (d, 2H,  $J = 6.0$ ), 7.19 (t, 1H,  $J = 8.3$ ), 6.99 (t, 1H,  $J = 2.1$ ), 6.83 (dd, 1H,  $J = 1.5, 7.8$ ), 6.58 (dd, 1H,  $J = 2.0, 7.8$ ), 6.28 (br s, 1H), 5.34 (s, 1H), 3.80 (t, 4H,  $J = 5.2$ ), 3.78 (s, 3H), 3.54 (s, 2H), 3.00 (s, 6H), 2.49 (t, 4H,  $J = 5.3$ ; ESI-MS  $m/z$ : 420 ( $MH^+$ ).

15 Example 148: 2-[4-(3-METHOXYBENZYL)-1-PIPERAZINYL]- $N^4$ -(3-METHOXYPHENYL)- $N^6,N^6$ -DIMETHYL-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedure S.  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.22 (d, 1H,  $J = 7.9$ ), 7.17 (t, 1H,  $J = 8.2$ ), 6.99 (t, 1H,  $J = 2.1$ ), 6.95 - 6.84 (m, 2H), 6.86 - 6.78 (m, 2H), 6.59 - 6.55 (m, 1H), 6.29 (br s, 1H), 5.32 (s, 1H), 3.82 (s, 3H), 3.79 (t, 4H,  $J = 5.1$ ), 3.77 (s, 3H), 3.52 (s, 2H),

2.99 (s, 6H), 2.49 (t, 4H,  $J = 5.1$ ); ESI-MS  $m/z$ : 449 (MH<sup>+</sup>).

5 Example 149:  $N^2$ -[2-(3-METHOXYPHENYL)ETHYL]- $N^4, N^4$ -DIMETHYL- $N^6$ -(4-METHYLPHENYL)-2,4,6-PYRIMIDINETRIAMINE:

Prepared by Procedure F (dioxane, potassium tert-butoxide, 120 °C, 16 h), Q (toluene, TEA, 120 °C), A (CH<sub>2</sub>Cl<sub>2</sub>, Δ, TEA). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.22 (t, 1H,  $J = 7.9$ ), 7.18 (d, 2H,  $J = 8.4$ ), 7.12 (d, 2H,  $J = 8.3$ ), 10 6.84 (d, 1H,  $J = 7.6$ ), 6.82 - 6.74 (m, 2H), 6.28 (br s, 1H), 5.28 (s, 1H), 4.77 (s, 1H), 3.80 (s, 3H), 3.63 (q, 2H,  $J = 6.7$ ), 2.99 (s, 6H), 2.89 (t, 2H,  $J = 7.4$ ), 2.32 (s, 3H); ESI-MS  $m/z$ : 378 (MH<sup>+</sup>).

15 Example 150:  $N^2$ -[2-(2-METHOXYPHENYL)ETHYL]- $N^4, N^4$ -DIMETHYL- $N^6$ -(4-METHYLPHENYL)-2,4,6-PYRIMIDINETRIAMINE:

Prepared by Procedures F (dioxane, potassium tert-butoxide, 140 °C, 16 h), Q (toluene), and A (CH<sub>2</sub>Cl<sub>2</sub>, Δ, TEA). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.23 - 7.12 (m, 4H), 7.12 20 (d, 2H,  $J = 8.1$ ), 6.89 (d, 1H,  $J = 7.8$ ), 6.86 (d, 1H,  $J = 7.6$ ), 6.61 (d, 1H,  $J = 8.0$ ), 6.50 (br s, 1H), 5.25 (s,